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# Brain structures subserving olfactory and visual learning and recognition: Similarities and differences in nonverbal memory processing

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**Dedication:**

This thesis is dedicated to my family, who always believed in me, and to my husband who was right – "I could do it".

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**Abstract**

The aim of these experiments was to investigate learning and memory extensively in two nonverbal domains (olfactory and visual), and to determine similarities and differences in the function of the neural substrates that subserve these modalities. Two complementary methodological approaches were taken: 1) examination of learning and retention in patients with resection from left (LR) or right (RR) temporal lobe, and 2) study of brain function via Positron Emission Tomography (PET) of healthy subjects during memory processing.

Two parallel recognition tests were developed (one olfactory, one visual) that examined memory at three stages: following a single exposure to test stimuli, after four exposures, and following a 24hr delay interval. In the olfactory patient study, LR and RR groups performed significantly worse than the healthy control subjects, with no difference between the patient groups; thus suggesting a lack of hemispheric superiority for this task. The PET study of healthy individuals supported the bilateral participation of piriform cortex during olfactory recognition. The results from these two studies, along with findings from animal work, suggest that the piriform cortices may play a role in odor *memory* processing, not simply in perception.

On the face memory task, LR and RR patients showed different results. Only RR patients were impaired, while LR patients did not perform differently from controls. This unique face learning paradigm was sensitive to right temporal lobe damage, and correctly classified patients by side of resection with a sensitivity rate of 82% and specificity rate of 79%, suggesting its possible utility as a clinical tool. PET face memory findings indicated greater participation of fusiform regions during long-term recognition, and

greater right prefrontal activity during short-term recognition, when these conditions are directly compared to each other.

Finally, PET was used to study the same healthy subjects performing parallel odor and face working-memory tasks, focusing on regions previously shown to be important for working memory. Results revealed similar regions of activation in dorsolateral prefrontal cortex in the two modalities. This indicates an overlap in the brain regions that process olfactory and visual information when the same cognitive manipulations are being carried out online.

**Résumé**

L'objectif de ces expériences était d'étudier en profondeur l'apprentissage et la mémoire dans deux domaines nonverbaux (olfactif et visuel), et de déterminer les similarités et les différences dans la fonction des substrats neuronaux responsables de ces modalités. Deux approches méthodologiques complémentaires ont été utilisées: 1) examen de l'apprentissage et de la rétention chez les patients avec resection du lobe temporal gauche (RG) ou droit (RD), et 2) étude de la fonction du cerveau par Tomographie par Émission de Positons (TEP) de sujets sains pendant le traitement mémoriel. Deux tests parallèles de reconnaissance ont été développés (un olfactif, un visuel) pour examiner la mémoire à trois étapes différentes: après un premier contact avec les stimuli du test, après quatre tels contacts, et après un intervalle de délai de 24 hres. Dans l'étude olfactive des patients, les groupes RG et RD obtinrent des résultats plus mauvais que les sujets contrôles sains, sans aucune différence entre les groupes de patients, suggérant ainsi l'absence de supériorité hémisphérique pour cette tâche. L'étude TEP d'individus sains a supporté la participation bilatérale du cortex piriforme pendant la reconnaissance olfactive. Les résultats de ces deux études, en plus des conclusions de tests chez l'animal, suggèrent que les cortex piriformes jouent peut-être un rôle dans le traitement de la mémoire olfactive, et non simplement dans la perception.

Pour la tâche mnésique sur les visages, les patients RG et RD manifestèrent différents résultats. Seul les patients RD furent affectés, alors que les patients RG eurent les mêmes résultats que les contrôles. Ce paradigme unique d'apprentissage de visage était sensible au dommage du lobe temporal droit, et classifia correctement les patients par côté de resection avec un taux de sensibilité de 82% et un taux de spécificité de 79%,

suggérant son utilité comme outil clinique. Les résultats TEP pour la mémoire de visages indiquent une plus grande participation des régions fusiformes pendant la reconnaissance à long-terme, et plus d'activité préfontale droite pendant la reconnaissance à court-terme, quand ces conditions ont été comparées directement.

Enfin, la TEP a été utilisée pour étudier les mêmes sujets sains complétant des tâches parallèles de mémoire de travail d'odeur et de visage, en portant attention aux régions dont l'importance à été démontrée pour ce type de mémoire. Les résultats ont mis en évidence des régions d'activation similaires dans le cortex préfrontal dorsolatéral dans les deux modalités. Ceci indique un chevauchement entre les régions du cerveau qui traitent l'information olfactive et visuelle quand les mêmes manipulations cognitives sont exécutées en ligne.

**Contributions of Authors**

McGill University requires that in the case of a manuscript based thesis an explicit statement of the contributions of each author must be made.

Paper 1 (Chapter 2): **Olfactory learning: Convergent findings from lesion and brain imaging studies in humans**

*Lauren A. Dade, Robert J. Zatorre & Marilyn Jones-Gotman*

Lauren Dade:

- Development of rationale and design of patient study in conjunction with M. Jones-Gotman
- Extensive pilot testing for experimental paradigm
- Subject recruitment, scheduling and testing
- Data entry and statistical analysis of behavioral data
- Development of PET study design in conjunction with M. Jones-Gotman and R.J. Zatorre
- Obtained approval from the MNI ethics committee for PET study
- Secondary analyses of PET data
- Interpreted results in conjunction with M. Jones-Gotman and R.J. Zatorre
- Presentation of study and results at international conferences
- Writing manuscript for journal submission

Robert Zatorre:

- Provided guidance in outlining the rationale and procedure for the PET study
- Assisted with PET data collection
- Gave valuable assistance and insights into the interpretation of the PET results
- Provided invaluable feedback and direction on manuscript revisions

Marilyn Jones Gotman:

- Played a valuable advisory and consultative role in the development of the olfactory memory testing paradigm
- Provided important feedback and assistance with subject selection criteria for the patient groups
- Assisted with the interpretation of the patient behavioral data
- Assisted with PET data collection and interpretation
- Provided guidance and excellent editing on paper revisions

Paper 2 (Chapter 3): **Face learning and recognition: a new paradigm to examine right hemisphere function**

*Lauren A. Dade & Marilyn Jones-Gotman*

Lauren Dade:

- Development of research design
- Acquisition of photographs for stimuli
- Creation of test stimuli and test procedure
- Extensive pilot testing for experimental paradigm
- Subject recruitment, scheduling and testing
- Data entry and statistical analysis of behavioral data
- Interpreted results in conjunction with M. Jones-Gotman
- Presentation of study and results at international conferences
- Writing of manuscript for journal submission

Marilyn Jones Gotman:

- Played a valuable advisory and consultative role in the development of the face memory testing paradigm
- Gave valuable input on development of stimuli
- Provided important feedback and assistance with the subject selection criteria for the patient groups
- Assisted with the interpretation of the patient behavioral data
- Provided guidance and excellent editing on paper revisions

Paper 3 (Chapter 5): **Working memory in another dimension: Functional imaging of human olfactory working memory.**

*Lauren A. Dade, Robert J. Zatorre, Alan Evans & Marilyn Jones-Gotman*

Lauren Dade:

- Development of research design
- Pilot testing of experimental paradigm
- Programming of computer for stimulus delivery and data collection
- Subject recruitment, scheduling and testing
- Data entry and statistical analysis of behavioral data
- Secondary analyses of PET data
- Interpreted results in conjunction with M. Jones-Gotman and R.J. Zatorre
- Presentation of study and results at international conference
- Writing manuscript for journal submission

Robert Zatorre:

- Instrumental assistance in experimental design
- Assisted with PET data collection
- Gave valuable assistance and insights into the interpretation of the PET results
- Provided invaluable feedback and direction on manuscript revisions

Alan Evans

- Provided the infrastructure and personnel necessary to complete this project
- Provided helpful editorial comments

Marilyn Jones Gotman:

- Gave valuable feedback in the design of the experimental paradigm
- Assisted with PET data collection
- Gave valuable assistance and insights into the interpretation of the PET results
- Provided excellent editing and advice with regard to manuscript revisions

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**List of Abbreviations:**

| | |
|---|---|
| CAH | Corticoamygdalohippocampectomy (type of surgical resection) |
| DFLT | Dade face learning test |
| FER | Fourth exposure recognition trial |
| fMRI | Functional Magnetic Resonance Imaging |
| IQ | Intelligence Quotient |
| LR | Group of patients with resection from the left temporal lobe |
| LT | Long-term recognition |
| MRI | Magnetic Resonance Imaging |
| NC | Control group of neurologically healthy participants |
| PET | Positron Emission Tomography |
| PC | Piriform Cortex |
| P350 | Evoked potential seen as a positive peak of around 350msec latency |
| rCBF | Regional Cerebral Blood Flow |
| RR | Group of patients with resection from the right temporal lobe |
| SAH | Selective amygdalohippocampectomy (type of surgical resection) |
| SER | Single exposure recognition trial |
| ST | Short-term recognition |
| WAIS-R | Wechsler Adult Intelligence Test-Revised |
| WRMT | Warrington Recognition Memory Test |

# Chapter One

## General Introduction

### Rationale

This series of experiments was designed to investigate learning and memory within two nonverbal memory domains: olfaction and vision (face memory). The specific goals were to examine the neural substrates that subserve memory function for these two modalities, and to determine if there were similarities and/or differences in how the underlying brain regions participate in memory function for these two types of stimuli. Two different complementary techniques were employed to study the contribution of different brain regions to memory function. As the temporal lobes are known to be important for memory (Meyer & Yates, 1955; Milner, 1968a; Milner, 1968b), the first experimental approach involved the study of patients who had excision from left or right temporal lobe regions for the treatment of intractable epilepsy. Examination of learning and retention in patients with a left or right resection would allow investigation of whether there are differences in learning patterns between the temporal lobes for these two types of nonverbal memory stimuli. The second experimental approach used the functional brain imaging technique of Positron Emission Tomography (PET) to determine brain regions that participate in odor and visual memory in healthy subjects.

By using these two methodologies, rather than either method alone, a more comprehensive view of how the brain functions during memory tasks could be obtained. Functional imaging of the healthy brain has the advantage of broadly revealing the brain areas that have a greater level of participation in one type of cognitive task as opposed to another. For example, one can examine the brain areas that are significantly more

involved in recognizing an odor smelled moments before, as compared to the brain activity that occurs when recognizing an odor smelled several days previously. Although this technique will reveal numerous areas that participate in this task, it does not indicate which regions are *necessary* for the normal completion of that task. Information from patient studies can shed light on this issue, because by virtue of the surgical resection, there are certain brain areas that no longer participate in cognitive processing. Thus, if patients are not able to complete a task within normal limits it is inferred that the excised brain area plays a critical part in this type of cognitive processing. One weakness of patient studies is that typically surgical excisions of brain tissue involve several different brain structures within a region (Trop, Olivier, Dubeau, & Jones-Gotman, 1997). Functional brain imaging findings can be of further assistance, as these data can reveal specific information about all the areas of activity that overlap with the region of resection in the patients. Thus, areas of overlap can delineate the brain structures critical for the cognitive task in question.

A planned combination of these two research methodologies creates a powerful research approach that has not been applied to olfactory memory previously. However, in order to assess olfactory learning and memory in this way, an appropriate testing paradigm needed to be invented that would be suitable for use with both research techniques, and that could also be applied to the development of an equivalent face memory test.

Learning Paradigm.

Jones-Gotman and colleagues (Jones-Gotman, 1986; Jones-Gotman et al., 1997; Majdan, Sziklas, & Jones-Gotman, 1996) have suggested that, not only are there material

specific memory deficits in relation to left and right temporal lobe damage, but that there may be differences in how each temporal lobe processes information. For example, patients with epileptic focus in the left temporal lobe do not always have a deficit in learning of verbal material, but they show a reliable and significant forgetting of verbal material after a delay interval. In contrast, patients with a focus in the right temporal lobe do have a deficit in learning of designs, but very little of the information is lost following a delay interval (Jones-Gotman, 1986; Jones-Gotman et al., 1997; Majdan et al., 1996). Their findings raised questions about whether this pattern may reflect basic differences in the mode of processing between the two temporal lobes, or whether their results for patients with right temporal lobe dysfunction were specific to abstract designs. I chose to pursue this question by using a learning paradigm with three recognition trials, using odors and faces as my nonverbal stimuli.

In this series of experiments (both olfactory and visual) the testing paradigm allowed an examination of memory after a single exposure to the test stimuli, a second recognition test after an additional three exposures, and assessment of retention via a final recognition test after a 24hr delay interval. There are several advantages to memory tests that examine performance over more than one trial. First, poor performance after a single presentation of stimuli can be due to secondary factors, rather than to a primary deficit in learning. For example, people may perform poorly due to attentional factors, or due to poor comprehension of the demands of the task. By testing subjects over multiple learning trials, one can evaluate an individual's ability to learn new material, and his or her ability to overcome a poor initial trial, if this occurs. Testing over multiple trials provides a 'learning context', and can give the examiner greater confidence in evaluating

poor initial performance. Combining this form of testing with an examination of long-term retention creates a more effective assessment paradigm that could help in clinically differentiating patients who have lesions in the left or right temporal lobe. Ultimately it will also allow me to determine if patterns of learning and retention for odors and faces are the same or different in patients with left or right temporal lobe dysfunction.

## Background for the olfactory memory studies

### Brief anatomical overview of cortical connections in the olfactory system

In the 1800's Hughlings Jackson remarked upon the relationship between the temporal lobe and olfactory function as inferred from case studies of patients with epilepsy arising from the anterior temporal lobe region, including the hippocampus and amygdala (Hughlings-Jackson & Beevor, 1889; Hughlings-Jackson & Stewart, 1899). These patients had seizures that were described as "uncinate fits" which had epigastric symptoms and crude, often unpleasant, olfactory auras. Later animal studies (See Haberly, 1985, and Shipley and Ennis, 1996, for review) and anatomical studies of the human olfactory system (Eslinger, Damasio, & Van Hosen, 1982; Price, 1990) supported the supposition that the anterior temporal region was important in olfaction. Odor information travels through the olfactory tract to the ipsilateral piriform cortex (the caudolateral aspect of the orbitofrontal cortex, at the frontotemporal junction, extending to the anterior dorsomedial aspect of the temporal lobe), anterior cortical nucleus of the amygdala, and the periamygdaloid and entorhinal cortices. These primary regions then make important connections to the hippocampus, ventral striatum, thalamus, and orbitofrontal cortex (see Carmichael, Clugnet, & Price, 1994, Eslinger et al., 1982, Price, 1990, and Shipley & Ennis, 1996, for review of anatomy). The secondary olfactory

cortex, in the orbitofrontal region, has been shown in humans and monkeys to be important for olfactory discrimination (Jones-Gotman & Zatorre, 1988; Potter & Butters, 1980; Takagi, 1986; Tanabe, Yarita, Iino, Ooshima, & Takagi, 1975; Zatorre & Jones-Gotman, 1991), and appears consistently in olfactory functional imaging studies (See Zald and Pardo, 2000, and Zatorre & Jones-Gotman, 2000, for review).

It is interesting to note that the olfactory system is not organized in a parallel fashion to the other senses, and therefore has certain unique factors (Herz & Engen, 1996). First, the olfactory receptor neurons are the only CNS neurons directly exposed to the environment, and unlike the mainly contralateral projections that occur with the other senses, projections from the receptor neurons to the anterior temporal lobe region are primarily ipsilateral. In addition, in all other sensory systems, information to the cortex is first routed through the thalamus: however, in the olfactory system, information coming from the olfactory receptors is routed to cortical brain regions without a thalamic relay. Therefore, this sensory information has the least number of synaptic relays from the receptor cells to the hippocampus and the amygdala, regions that are important for memory. This close link to memory structures may contribute to odors acting as more effective contextual memory cues than other types of stimuli (Herz, 1997), and may contribute to their ability to elicit more emotionally laden memories (Herz & Cupchik, 1995). However, although the olfactory system connects intimately with temporal-lobe structures known to be important for memory (Meyer & Yates, 1955; Milner, 1968a; Milner, 1968b), it is not clear what regions are most important for olfactory memory, and whether there is a hemispheric asymmetry for olfactory memory as there is for memory for other types of material.

Olfactory memory studies in patients with brain lesions

A number of studies examining olfactory function in patients with known brain lesions have been carried out. However, overall the findings have been mixed: some studies suggest a left hemisphere advantage, some suggest a right hemisphere superiority, and others suggest a more equivalent level of importance of the two hemispheres in different olfactory tasks.

Several olfactory memory studies have shown deficits in patients with epilepsy arising from either the left or right temporal lobe. Savic and colleagues (Savic, Bookheimer, Fried, & Engel, 1997) studied unoperated patients with epilepsy arising either from mesial temporal lobe (MTL) structures, or from temporal neocortical areas. Patients with MTL seizures performed significantly worse than healthy control subjects on an odor memory task. There was no significant difference in odor memory performance between patients with neocortical versus MTL seizures, and there was no difference between patients with seizures arising from the left versus right MTL. Martinez et al. (1993) using a monorhinal recognition paradigm, found no significant difference between left and right temporal-lobe epilepsy patients in preoperative performance; the combined group of patients performed significantly worse than the healthy control subjects on discrimination and memory. An analysis of change of pre- to postoperative memory scores in these same patients showed no significant differences, but there was a slight trend for a right resection/right nostril decline in recognition performance after surgery. A study carried out by Eskenazi and colleagues (Eskenazi, Cain, Novelly, & Friend, 1983), using a two-item forced choice recognition procedure, found that patients with left or right temporal lobe lesions were impaired on odor

memory, with no significant differences between the two groups. In a second study, using a monorhinal recognition paradigm, Eskenazi et al (Eskenazi, Cain, Novelly, & Mattson, 1986) again found that both groups of patients with resection from a temporal lobe performed significantly worse than controls. However, the deficit was limited to performance with the nostril ipsilateral to the side of excision. Unoperated epilepsy patients were also tested using this same paradigm but they did not show an odor memory deficit. In another study by Rausch et al (Rausch, Serafetinides, & Crandall, 1977), both left and right postoperative groups were impaired on odor recognition. However, in this instance the right temporal resection patients were significantly more impaired than patients with resection from the left temporal lobe.

Although there have been findings of olfactory impairment occurring with either left or right temporal lobe dysfunction, other studies have suggested a hemispheric superiority. For example, one study (Henkin, Comiter, Fedio, & O'Doherty, 1977) found that patients with a left temporal lobe resection had a greater odor recognition deficit than patients with a right resection. However, among studies that suggest hemispheric superiority for odor memory, a greater number have shown a deficit restricted to patients with disturbance within the right hemisphere, while patients with disturbance within the left hemisphere perform within the normal range. Abraham and Mathai (1983) using an odor matching paradigm, found that patients with a right temporal lobe disturbance (including patients with either right temporal lobe resection, or unoperated patients with right temporal EEG epileptiform abnormalities) were impaired compared to both healthy control subjects and patients with a left temporal lobe disturbance. There was no significant difference between patients with interference within the left temporal lobe and

healthy control subjects. Jones-Gotman and Zatorre (1993) examined olfactory memory in eight groups of patients, including those with excision from a left or right temporal lobe, left or right frontal lobe, and right frontotemporal region. On a dirhinal yes-no recognition test, among the patients with resection from a temporal lobe, only those with a small excision from the right hippocampus were impaired. Of the frontal and frontotemporal patients, only the patients with lesions in the right hemisphere were impaired. In addition, patients with a right orbitofrontal lesion performed worse than patients with the orbital region intact. However, one must take into account that the orbitofrontal region is important for olfactory discrimination, and poor performance on the part of these patients may be due to perceptual discrimination deficits, which would supercede a recognition memory deficit.

Support for right hemisphere superiority in odor processing

In concert with findings suggesting greater right hemisphere involvement, several other studies examining different types of olfactory processing have suggested a right hemispheric superiority for olfaction. Zucco and Tressoldi (1989) studied hemispheric lateralization for olfactory processing in healthy subjects using tachistoscopic presentation of pictures and names, which had to be judged as matching (or not matching) an earlier presented odor. They found faster reaction times when the visual items were presented to the right hemisphere via the left visual field, which was interpreted as a priming effect of the right hemisphere by the odors. This left visual field effect was quite robust, as it was present even when the visually presented materials were *names* of the odors, which would be thought to engage the left hemisphere quite strongly. Also, Zatorre and Jones-Gotman (1990) showed a right nostril advantage for olfactory

discrimination within a population of healthy subjects (although it was not observed for each individual). A patient study that looked at olfactory discrimination with the same task showed deficits ipsilateral to the side of resection, except that patients with a right orbitofrontal lesion were impaired in both nostrils (Zatorre & Jones-Gotman, 1991). Due to the small number of subjects with a *left* orbitofrontal excision the impact of this lesion, and hence the role of this area in olfaction, remain less clear. Nonetheless, the findings of a special role for the right orbitofrontal region, and for a greater role of the right hemisphere in olfaction, are supported by findings of a positron emission tomography (PET) study of healthy individuals passively smelling odors (Zatorre, Jones-Gotman, Evans, & Meyer, 1992). In this study, activation was noted bilaterally in piriform areas and in the right orbitofrontal region, and their findings of significant right orbitofrontal activity during olfactory tasks has since been replicated across several more recent studies (See Zald and Pardo, 2000, and Zatorre & Jones-Gotman, 2000, for review).

Issues of olfactory memory test design

The point of interest in my olfactory memory study is recognition of the actual scents presented, rather than recognition or recall of the labels of the odors. The distinction between these two forms of remembering an odor are very important in studies of patients, where some groups may be impaired in the verbal memory sphere and others are not. Some studies have emphasized odor recall, where essentially subjects have to generate and remember the names of odors they have smelled (Jehl & Murphy, 1998; Murphy, Nordin, & Acosta, 1997; Nordin & Murphy, 1998). However, when comparing groups that have different degrees of verbal memory impairment, the verbal component of the task can cloud the findings with respect to how well subjects can

remember the actual odors. For instance, patients with lesions of the speech dominant left temporal lobe are known to have verbal memory deficits (Meyer & Yates, 1955; Milner, 1958). These types of subjects are likely to have difficulties generating and remembering the *names* of odors they have smelled. Therefore at the time of odor 'recall', when they have to state the names of previously presented odors, they may perform poorly, but due to a verbal deficit rather than an olfactory deficit. On the other hand, patients who have an olfactory memory deficit may be helped by the use of verbal labelling. They may depend solely on the verbal tag they created and rely on memory of the odor label in order to do the task. This results in an amelioration of their performance and concealment of their olfactory deficit. Hence, the issue of verbal coding in terms of its implementation by subjects, and effects on odor recognition, requires careful consideration in odor memory study design.

Development of the olfactory test

In the choice of stimuli for my odor memory test, I wanted to avoid a labelling confound. To decrease the usefulness of applying general category labels to the odors that were to be learned (the target odors), I used target and recognition foil odors from the same general category. Hence, if a subject used a general category label of 'minty' for the eucalyptus scent, during the recognition test a different minty scent would be presented and the subject would have to decide on the basis of the actual aroma whether the minty scent being smelled was the target odor or not.

Test development commenced with 12 sets of four odors arising from 12 veridical categories (48 odors in total). Extensive pilot testing was carried out on 120 healthy subjects to determine the discriminability of each odor within its own category and

between odors in the next ecologically close category (e.g. fruity odors and citrus odors). Target odors were chosen based on their high discriminability from other odors within the same category and from odors in the ecologically close category. Descriptions of the testing procedure and the results can be found in the method section of the olfactory memory manuscript (Chapter 2).

Overall aim of the olfactory experiments

The two experiments described in Chapter 2 were designed to examine odor learning and recognition in healthy subjects as well as in patients with excision from left or right temporal-lobe regions. There were three major goals for these studies: 1) to elucidate brain regions that were important for odor encoding, recognition, and long-term retention, 2) to evaluate if differences in learning patterns occur between subjects with excision from the left or right temporal lobe, and 3) to determine if there was a right temporal-lobe superiority for odor memory as has been indicated for other types of nonverbal tasks (Barr, 1997; De Renzi & Spinnler, 1966; Jones-Gotman, 1986; Jones-Gotman et al., 1997; Milner & Taylor, 1972; Warrington & James, 1967), and has been found in some odor memory experiments (Abraham & Mathai, 1983; Jones-Gotman & Zatorre, 1993).

## Background for face memory studies

I had chosen faces as the stimuli for the second type of nonverbal material in my learning experiments. The literature suggests a right hemisphere predominance in cerebral processing for both olfactory and visual stimuli, while in both cases there is evidence contrary to this notion. For instance, in the face literature, recent studies using established face recognition tests have failed to show accurate classification of patients

with disturbance in left or right temporal lobe based on their face memory performance (Hermann, Connell, Barr, & Wyler, 1995; Kneebone, Chelune, & Luders, 1997; Naugle, Chelune, Schuster, Lüders, & Comair, 1994). I hoped to clarify questions of laterality by examining possible differences in learning and retention patterns between left and right patient groups, using a new testing paradigm that may be more sensitive to face memory processing by virtue of its ability to assess memory over several trials.

Lateralization of face memory

Early face experiments showed that patients with damage within the right hemisphere had greater face recognition impairment than patients with left hemisphere dysfunction (Benton & Van Allen, 1968; De Renzi & Spinnler, 1966; Milner, 1968b; Warrington & James, 1967). This finding has been given further support from structural brain imaging studies of patients who are impaired in face perception and/or recognition (prosopagnoisia), showing damage restricted to the right hemisphere (De Renzi, Perani, Carlesimo, Silveri, & Fazio, 1994; Takahashi, Kawamura, Hirayama, Shiota, & Isono, 1995). More recently, functional imaging studies of face perception and recognition have revealed a region within the extrastriate cortex that increases in activity when subjects are viewing faces (fusiform face area, or FFA) (Allison et al., 1994; Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999; Haxby et al., 1994; Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Gore, & Allison, 1997) and this area is detected more consistently across subjects in the right rather than left FFA (Kanwisher et al., 1997).

However, although there is support for a right hemisphere specialization for face memory, there is information to suggest that the left hemisphere may also play a role. In an interesting study of patients who had undergone a cerebral commisurotomy, Levy and

colleagues (Levy, Trevarthen, & Sperry, 1972) were able to show that hemispheric superiority for face perception could shift between the left and right hemispheres depending on the response demands of the task (pointing versus naming). Also models of face recognition (Bruce, 1983; Rhodes, 1985) suggest that the left hemisphere contributes to face learning by processing important semantic information related to the individual, such as name, occupation and personal history. Indeed, in functional imaging studies, regions within the left temporal lobe have been shown to be more active during the recognition of famous faces versus the recognition of famous names (Tempini et al., 1998), and more widespread bilateral activity has been noted during the recognition of famous faces as compared to faces seen for the first time (Leveroni et al., 2000). Therefore, although some research does suggest right hemisphere, and particularly right temporal lobe, specialization for face memory (Baxendale, 1997; Milner, 1968b; Morris, Abrahams, & Polkey, 1995; Warrington, 1984), the left hemisphere may participate to a greater extent on different types of face memory procedures.

The question of laterality of function for face memory is also raised due to findings of recent clinical memory studies. These studies indicate that current face memory tests have poor classification abilities amongst unoperated left or right temporal lobe epilepsy patients (Hermann et al., 1995; Kneebone et al., 1997; Naugle et al., 1994). Although initially this may suggest a lack of specialization for face memory, there are several explanations as to why unoperated patients may not show the differences that occur in patients following resection from a temporal lobe. One possibility is that in unoperated patients the brain region that subserves face memory, although dysfunctional, may still be contributing to face processing to some extent. For instance, if the right

temporal lobe region is important for face memory, and it is still functioning, although not optimally, it may be able to maintain adequate face recognition as tested by current single-trial test paradigms. However, if this region is not functioning optimally, some deficits should be observed if the test is of adequate difficulty, and if different stages of memory processing are examined.

It was hoped that the face memory test that I designed would have good classification sensitivity and specificity, and would later prove to be useful in the clinical evaluation of neurological patients.

Development of the face test

Initial pilot testing for this new face memory test demonstrated that healthy subjects learned faces very easily. Therefore, a unique approach was taken to create a test that would be of sufficient difficulty to assess learning, and yet still parallel the olfactory memory test. Twelve sets of faces were created using a computer software program (Knoll, Hamburg, & Pawliger, 1994) to alter the facial configuration of 12 original photographs of faces (described in Chapter 3). Three altered versions of each face were devised, resulting in a total of 48 faces. Twelve faces were chosen as target stimuli and the others served as recognition foil stimuli across three recognition conditions (recognition following one exposure, following four exposures, and following a 24hr delay interval). By using target and foil faces that closely resembled each other, the task difficulty was increased to a level appropriate to test learning (as determined by pilot testing on 154 undergraduate students). In addition, the paradigm matched that of the olfactory task precisely. The exact development and design of the face learning and recognition test are described in detail in the second manuscript (Chapter 3).

Application to functional imaging

The second face memory experiment employed PET imaging to compare levels of brain activity during face encoding, short-term recognition and long-term recognition. The comparison of these conditions to each other provided a control, in that subjects were observing faces for all imaging conditions. Thus, the only substantial differences to be found should be related to the specific cognitive processes required (encoding versus recognition) (Fox, Mintun, Reiman, & Raichle, 1988). This PET experiment used a modified version of the face learning test used in the patient experiment, allowing clear comparisons between these two studies. This experiment is discussed in Chapter 4.

Overall aim of the face memory experiments

The two initial goals of the patient face memory experiment were to examine patterns in face learning and retention between patients with left or right temporal lobe resection, and to then compare these findings with those of the olfactory memory patient study. The clinical utility of the test was also examined, to determine if results could be used to correctly classify individual patients to their side of resection. The aim of the complementary PET study was to investigate possible differences in lateralization of brain function on this face memory test and evaluate differences in activity during face encoding, and short-term and long-term recognition. These findings would also be integrated with those from the patient study. The similarities and differences in performance of the patient groups on the odor and face memory tests will be presented in the general discussion (Chapter 6).

## Working memory

The final study of this thesis is an examination of the brain regions that subserve olfactory working memory. Although there have been many studies that have examined working memory in the visual and verbal domains (Barch et al., 1997; Braver et al., 1997; Cohen et al., 1994; Cohen et al., 1997; Courtney, Ungerleider, Keil, & Haxby, 1996; D'Esposito et al., 1995; Faillenot, Sakata, Costes, Decety, & Jeannerod, 1997; Owen et al., 1998; Petrides, Alivisatos, Evans, & Meyer, 1993a; Petrides, Alivisatos, Meyer, & Evans, 1993b), none have examined olfactory working memory. The model of working memory introduced by Baddeley (Baddeley, 1986) consists of a central executive processor, which acts as an attentional control, and two slave systems that hold and manipulate information. These two slave systems are the *phonological loop*, which registers and stores verbal information, and the *visuospatial sketchpad*, which consists of an object and a spatial processor. Interestingly, working memory in other modalities such as olfaction and taste is not addressed in this model.

Prefrontal cortex is known to subserve working memory processing, however, the functional division of the dorsolateral and ventrolateral prefrontal cortex is currently under debate (Owen, 1997; Ungerleider, Courtney, & Haxby, 1998). The domain specific model of working memory suggests that the regions of the frontal cortex are divided based on the type of information that is being processed: the dorsolateral prefrontal regions are important for spatial working memory, and ventrolateral regions are important for nonspatial working memory (the equivalent of the object processor) (Goldman-Rakic, 1995). Another model, the 'two-level hypothesis' of the functional division of dorsolateral and ventrolateral prefrontal cortex, is based upon the type of

cognitive process that is to be carried out, rather than the type of material that is being processed (although this issue is also addressed) (Petrides, 1994; Petrides, 1995). In this model, dorsolateral prefrontal cortex is important for the ongoing monitoring and manipulation of information that is currently being held 'on-line', and the ventrolateral region is important for the active encoding and retrieval of information that is held in posterior cortical association areas. In the two-level model, it is the type of cognitive process that is being carried out that is crucial in determining the participation of dorsolateral versus ventrolateral regions. In addition, the two-level hypothesis does not exclude the possibility of modality specific regions, suggesting that small modality-specific regions may occur *within* the dorsolateral and ventrolateral regions. Therefore it may be possible that a region in the dorsolateral prefrontal cortex is specialized in the manipulation of 'online' olfactory information, and a region in the ventrolateral cortex is specialized in the retrieval of related olfactory information from posterior association regions.

Functional brain imaging (PET)of healthy subjects was used to examine these working memory issues with regard to the olfactory modality. The question was raised as to whether olfactory working memory would rely on prefrontal regions, and if so, would it utilize these regions to the same extent as a visual working memory paradigm. In order to address this second question, these same subjects participated in a face working memory task that required the same monitoring and manipulation demands as the olfactory task. In relation to the domain specific working memory model, when compared to their appropriate sensorimotor control task, neither of these two working memory tasks should show significant increases in activity in the dorsolateral prefrontal

region, as neither task requires spatial monitoring. Alternatively, the two-level processing hypothesis would predict increased activity in dorsolateral prefrontal regions for both of these tasks (in comparison to a sensorimotor control task), as both tasks have the same requirements of stimulus monitoring and manipulation. Further discussion of these working memory theories and the results of the current study are presented in the final manuscript (Chapter 4).

## Conclusion

This series of studies presents a comprehensive investigation of memory processing for two different kinds of nonverbal stimuli: odors and faces. Several advantages are obtained by using parallel testing paradigms for two different types of material. Direct comparisons between performance on the olfactory and visual tasks can be made easily, as both the olfactory and face tests measure memory processing at the same stages and use the same recognition response format. In addition, both tasks are applied to the same patient groups. Therefore, meaningful interpretations can be made of the similarities and differences that occur in patient performance for these two types of memory tasks. For a general discussion of these points see Chapter 6.

Advantages are also obtained by applying a similar testing paradigm in two complementary research methodologies (studies of patients with temporal lobe lesions and functional brain imaging of healthy subjects). Greater insights into the function and participation of specific brain regions can be obtained through the comparison of patient and PET results than through the use of either method alone.

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## Chapter Two

# Olfactory learning:

# Convergent findings from lesion and brain imaging studies in humans

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Submitted to *Brain*

Abstract

The role of temporal-lobe structures in olfactory memory was investigated by 1) the examination of odor learning and memory in patients who had undergone resection from a temporal lobe (including primary olfactory regions) for the treatment of intractable epilepsy and 2) the examination of brain function during odor memory tasks as assessed via positron emission tomography (PET) imaging of healthy individuals. In order to study different stages of odor memory, recognition of a "list" of odors was tested after a first exposure, again after four exposures, and once more after a 24hr delay interval. Patients with resection from a temporal lobe performed significantly worse than control subjects on all trials, and no significant differences were noted as a function of side of resection, indicating that there is not a strong hemispheric superiority for this task. The PET data yielded different levels of activity in piriform cortex (primary olfactory cortex), in relation to the 'no-odorant' baseline scan, depending on the type of processing: no increase in activity noted during odor encoding, a small increase bilaterally during short-term recognition, and a larger increase bilaterally during long-term recognition. These findings, along with findings in animal studies, suggest that piriform cortex may have an active role in odor *memory* processing, not simply in odor perception. Combined, the findings from the lesion study and functional brain imaging of healthy subjects suggest that olfactory memory requires input from both temporal-lobe regions for optimal odor recognition, and that unlike with verbal or nonverbal visual material, there is not a strong functional lateralization for olfactory memory.

The current understanding of brain regions involved in human olfactory memory is based upon findings from animal studies [see Haberly (1985) and Shipley and Ennis (1996) for review], human anatomical investigations (Price, 1990), as well as from human brain lesion research [see West and Doty (1995) for review]. Although there are currently a number of olfactory imaging studies [see Zatorre and Jones-Gotman (2000) and Zald and Pardo (2000) for review], none have looked at encoding, or at short-term versus long-term recognition of learned odors. Our purpose therefore was to investigate these aspects of olfactory memory through a convergent approach of examining patients with resection from temporal lobe structures as well as studying these same aspects in the healthy brain, through the use of positron emission tomography (PET).

As early as the 1800's, the relationship between human olfactory function and the temporal lobe region was raised in the context of olfactory auras and olfactory dysfunction noted in temporal lobe epilepsy patients (Hughlings-Jackson & Beevor, 1889; Hughlings-Jackson & Stewart, 1899). Anatomical studies in mammals have shown that the olfactory tract projects ipsilaterally to the piriform cortex (the caudolateral aspect of the orbitofrontal cortex, at the frontotemporal junction, extending to the anterior dorsomedial aspect of the temporal lobe), anterior cortical nucleus of the amygdala, and the periamygdaloid and entorhinal cortices: all but the orbitofrontal region are temporal lobe structures. From these primary regions there are important connections to the hippocampus, ventral striatum, thalamus, and rostral orbitofrontal (area 11) cortex [see Carmichael, Clugnet, & Price, (1994); Eslinger, Damasio, & Van Hosen, (1982); Price, (1990); Shipley & Ennis, (1996) for review of anatomy]. However, although the olfactory system connects intimately with temporal-lobe structures known to be

important for memory (Meyer & Yates, 1955; Milner, 1968a; Milner, 1968b), it is not clear what specific regions within temporal cortex are most important for *olfactory* memory. Also it is unclear whether there is a hemispheric asymmetry for olfactory memory as has been found to be the case in studies of other types of materials (Jones-Gotman et al., 1997b; Meyer & Yates, 1955; Milner, 1958; Milner, 1968b).

Several studies have examined olfactory memory in groups of temporal lobe epilepsy patients. But, the results have been unclear as to whether a greater olfactory memory impairment occurs with left or right temporal-lobe dysfunction. Thus, one study of unoperated epilepsy patients found that patients were not impaired on a monorhinal odor recognition paradigm (Eskenazi, Cain, Novelly, & Mattson, 1986), while two other studies showed odor memory impairment in patients who had epilepsy arising from either temporal lobe (Martinez et al., 1993; Savic, Bookheimer, Fried, & Engel, 1997). Consistent with the latter findings, three studies of operated patients showed impairments after resection from either the left or the right temporal lobe (Eskenazi, Cain, Novelly, & Friend, 1983; Eskenazi et al., 1986; Rausch, Serafetinides, & Crandall, 1977). Interestingly, the study by Eskenazi et al. (Eskenazi et al., 1986), using a monorhinal recognition paradigm, showed that the recognition deficits in these patients were confined to the nostril ipsilateral to the side of the temporal-lobe lesion. Also, the study by Rausch et al. (Rausch et al., 1977) hinted at a greater role of the right temporal lobe in odor memory: although both patient groups were impaired, those with a right resection were significantly more impaired than patients with a left resection. In contrast, Henkin, Comiter, Fedio, and O'Doherty (1977) found that patients with excision from the left

temporal lobe performed worse on an odor recognition test than patients with a right resection.

Support for greater right hemisphere involvement has come from studies finding odor memory impairment restricted to patients with damage in the right hemisphere (Abraham & Mathai, K. V.., 1983; Carroll, Richardson, & Thompson, 1993; Jones-Gotman & Zatorre, 1993). Additional support for a right hemisphere advantage in olfactory function arises from other non-memory olfactory findings, such as a right nostril/right hemisphere advantage for detection (Cain & Gent, 1991) and discrimination (Zatorre & Jones-Gotman, 1990; Zatorre & Jones-Gotman, 1991), and a right hemisphere priming effect for odor naming (Zucco & Tressoldi, 1989). The more consistent findings of right hemisphere superiority in these other olfactory processing tasks have given weight to hypotheses about right hemisphere dominance for olfactory memory. Nevertheless, studies to date have failed to provide consensus for the proposed model of right-hemisphere superiority in odor memory.

One tool that can aid in the investigation of this question of hemispheric specialization for olfactory memory is functional brain imaging. By combining this approach with the study of brain-lesioned patients, it is possible to determine the structures that participate in olfactory memory in the healthy brain through imaging, and learn what regions are *necessary* to perform the task within normal limits through the observation of patients with surgical lesions. Although PET has been used to study other olfactory functions, potential differences in brain activity during encoding and long-term recognition have not been examined.

Before presenting the testing approach used in the current study, the issue of verbal labelling in the context of odor memory experiments needs to be discussed. Although odors are known to be difficult to label (Cain, 1979; Richardson & Zucco, 1989; Schab, 1991), and some studies have suggested that verbal elaboration has little positive effect on odor memory (Engen & Ross, 1973; Lawless & Cain, 1975), many other studies have shown memory improvements when subjects are required to label odors (or are given odor names) during learning (Jehl, Royet, & Holley, 1997; Jones-Gotman & Zatorre, 1993; Lehrner, Gluck, & Laska, 1999a; Lehrner, Walla, Laska, & Deecke, 1999b; Lyman & McDanial, 1986; Lyman & McDaniel, 1990; Rabin & Cain, 1984; Walk & Johns, 1984). But, when subjects are left to their own encoding strategies, they do not perform as well as when asked to provide an odor name, or to give other types of associations when they first smell the odor. These findings suggest that subjects do not naturally attempt to label odors in the same way as when asked to label odors explicitly, and that initially odors may be encoded largely as perceptual entities (Engen & Ross, 1973; Lawless & Cain, 1975; Rabin & Cain, 1984; Walk & Johns, 1984; White, Hornung, Kurtz, Treisman, & Sheehe, 1998).

The possibility that verbal factors influence olfactory memory performance is an important one to consider in patient studies. If subjects are able to generate and rely on a verbal tag for even some of the odors that they are able to recognize, this would provide them with an advantage over patients who are unable to make and maintain this additional memory cue. For example, patients with left temporal lobe lesions are known to have verbal memory deficits (Meyer & Yates, 1955; Milner, 1958). Therefore if the use of odor labels is practical, or if emphasized within an odor memory paradigm,

patients without a verbal memory deficit may have an advantage, regardless of their ability to remember the actual odor quality of a previously presented scent.

To decrease the effectiveness of an odor labelling strategy, a recognition test that did not encourage labelling, but depended on an accurate odor memory, was developed. This was made possible by using different odor categories and multiple odors arising from each category as stimuli. The subjects would have to recognize specific odors they had smelled before from among other odors that derived from the same general category, making the use of general verbal tags ineffective. This approach in odor selection for target and foil stimuli was applied to a behavioral testing paradigm that examined olfactory recognition after: (1) a first exposure (a measure of initial encoding), (2) short-term recognition after four exposures (to examine learning) and (3) long-term recognition after an extended delay interval, to study retention.

The odor memory test was designed for behavioral testing of patients and healthy control subjects, and was adapted for use in a PET research design that would examine healthy brain activity during the same cognitive processes of odor encoding and recognition. Areas anticipated to show increased activity during the odorant-present tasks (encoding and recognition) as compared to the "no-odorant" control task, included the primary (piriform) and secondary (right orbitofrontal) olfactory cortices. Although early PET findings suggested that activity in primary olfactory cortex (bilateral piriform) represented basic sensory processing and would therefore be present during all odor processing tasks (Zatorre, Jones-Gotman, Evans, & Meyer, 1992), later studies have shown inconsistent levels of piriform activity that cannot be explained simply by differences in research methodology [see Zatorre and Jones-Gotman (2000), and Zald and

Pardo (2000) for discussion]. Thus, the presence or absence of activity within piriform cortex would be of interest. Possible differences in activation between left and right prefrontal regions during odor encoding versus recognition was also of interest, as several different hypotheses about their participation in encoding and retrieval of material have arisen (Buckner & Koutstaal, 1998; Frey & Petrides, in press; Kelley et al., 1998; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994; Wagner, Desmond, Glover, & Gabrieli, 1998). For example, some researchers claim that the left prefrontal cortex is more involved in episodic encoding, while right prefrontal regions are involved in episodic retrieval (Hemispheric Encoding and Retrieval Asymmetry, or 'HERA', model) (Buckner, 1996; Tulving et al., 1994). Others suggest that the differentiation of function between left and right prefrontal regions is dependent on the type of material to be encoded (verbal vs. nonverbal) (Kelley et al., 1998). Differences in areas of activity between short- and long-term recognition conditions were also of interest, as in other tasks prefrontal regions have been shown to be preferentially involved in short-term as opposed to long-term memory processing (Dade, Zatorre, & Jones-Gotman, submitted; Dade, Zatorre, Jones-Gotman, & Evans, 1997a). Additionally, areas of temporal-lobe activity detected by PET would be compared to the area of brain resection in the patient study, as we predicted that areas showing increased activity during odorant-present PET conditions would correspond to regions which, when resected in patients, result in disruption of olfactory memory processing. Portions of these data have been presented previously in abstract form (Dade, Jones-Gotman, Zatorre, & Evans, 1998).

Study I: Olfactory memory in patients with resection from a temporal lobe

## Methods

### Subjects

Forty patients who had undergone unilateral resection from the left (n=21) or right (n=19) temporal lobe for the treatment of intractable epilepsy, and 21 healthy normal control subjects (NC) matched approximately for sex, age, education, and smoking habits (Table 1) participated in this study.

Table 1. Subjects

| Group | *n* | Mean age *(range)* | Mean years of education *(range)* | Mean IQ *(range)* | Sex *(W, M)* | Smokers *(n)* |
|---|---|---|---|---|---|---|
| LR | 21 | 35.0 (22-48) | 14.3 (10-20) | 104 (84-126) | 6, 15 | 6 |
| RR | 19 | 37.3 (22-55) | 13.4 (10-20) | 98 (82-120) | 12, 7 | 4 |
| NC | 21 | 35.1 (19-57) | 13.9 (11-17) | - | 10, 11 | 7 |

LR = left resection
RR = right resection
NC = normal control

In all cases, the origin of the patient's epileptic seizures had been localized to a single focus as determined by EEG, magnetic resonance imaging (MRI), and clinical findings. All except for four patients were right handed; the left-handed patients had been shown by preoperative intracarotid amobarbital testing (Branch, Milner, & Rasmussen, 1964) to have speech representation in the left cerebral hemisphere. All patients were of normal intelligence with Full Scale WAIS-R IQ (Wechsler, 1981) ratings above 80. Analysis of

variance did not demonstrate any significant differences in age or education level among the three groups, and no significant difference in Full Scale IQ ratings between the two patient groups (Table 1). This study was approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital. All subjects gave informed written consent.

Patients had undergone one of two different surgical approaches, both involving removal of mesial temporal lobe brain structures. The majority of patients [left resection (LR) = 15; right resection (RR) = 13] underwent a corticoamygdalohippocampectomy (CAH), or anterior temporal lobe resection. The surgical CAH approach consists of a neocortical resection (averaging between 4.5- to 5.0-cm along the Sylvian fissure, extending to the level of the precentral sulcus), partial to complete resection of amygdala, and varying extents of excision from hippocampus and parahippocampal gyrus (ranging from 0.5cm to approximately 3 cm) (Trop, Olivier, Dubeau, & Jones-Gotman, 1997). The remaining 12 patients (LR = 6; RR = 6) underwent a selective amygdalo-hippocampectomy (SAH). This approach involves making a small 2- to 3-cm excision through the second temporal gyrus, just below the superior temporal sulcus. The sulcus is followed down to the floor of the lateral ventricle, where resection of the amygdala (partial to complete) and hippocampus (0.5cm –2.5cm) takes place, leaving the neocortex relatively intact (Trop et al., 1997).

Determination of the exact extent of an individual patient's resection is difficult, and intraoperative reports often overestimate the area removed (Awad et al., 1989). Therefore, for the purpose of verification of the area of surgical excision, measurements of the resection were made by examining postoperative T1-weighted MRI scans obtained

using 1mm slice acquisition. Of the patients participating in the study, 21 had the appropriate scan available for measurement (LR = 10; RR = 11). Each scan was transformed into Talairach space (Talairach & Tournoux, 1988) using an automated algorithm (Collins, Holmes, Peters, & Evans, 1994). Measurements were taken by progressing coronally along the *y* axis through each millimetre slice image of the entire brain scan. The extent of remaining tissue of the hippocampus, and entorhinal and parahippocampal cortices was calculated as the length of the structure from the most rostral point of intact tissue to the most caudal point (Crane, 1999) (See Table 2). A gross approximation of the extent of excision from the amygdala was made by a visual comparison to the unoperated hemisphere and estimating the percentage of tissue that was remaining. In the CAH patients, the extent of *removal* along the superior and inferior temporal gyri was estimated as the difference between the *y* coordinate of the intact temporal pole and the *y* coordinate of the posterior most point of the lesion. The extent of excision averaged 22mm along the superior temporal gyrus (range: 5-50mm) and 43 mm along the inferior temporal gyrus (range 29-70mm).

Precise anatomical landmarks for the anterior and posterior borders of the piriform cortex, which can be determined from an MRI scan, have not been defined. However we wanted to be able to quantify the extent of resection within this region in the patients for whom we had MRI scans. Therefore, we chose a novel approach of estimating the extent of piriform excision by identifying it via the existing functional imaging information about the piriform area activations that occur during smelling. Thus the piriform region was identified by utilizing the averaged PET coordinates for piriform activity obtained from the current PET study, and the studies of Small, Jones-Gotman,

Zatorre, Petrides and Evans, (1997), Sobel et al. (1998), Zatorre et al. (1992), and Zatorre, Jones-Gotman and Rouby (2000) [see Zatorre and Jones-Gotman (2000) for discussion]. The limits of left and right piriform regions were defined as two standard deviations above and below the average left ($x$ = -21, $y$ = 5, $z$ = -19; *s*: $x$ =2, $y$ = 4, $z$ = 3) and right ($x$ = 21, $y$ = 4, $z$ = -14; *s*: $x$ =3, $y$ = 6, $z$ = 1) Talairach coordinates (Talairach & Tournoux, 1988), of PET piriform activity. Using our patient MRIs transformed (Collins et al., 1994) into Talairach space (Talairach & Tournoux, 1988), we were able to examine each coronal MRI image at 1mm intervals between the two standard deviations above and below the $y$ coordinate for the left and right piriform cortices. At each one millimetre coronal slice image the medial, lateral, superior and inferior margins of the piriform area (as determined by the two standard deviations above and below the averaged $x$ and $z$ coordinates) were examined to determine if tissue was present or excised. The number of coronal slices where piriform was intact were then added together as total intact millimetres and divided by the total extent of the piriform region in the coronal plane as identified by the PET measurements (left piriform total coronal extent = 18mm; right piriform total coronal extent = 24mm). The percentage of intact piriform tissue within the specified range is reported in Table 2.

All patients had removal from the mesial temporal lobe structures (amygdala, hippocampus, entorhinal and parahippocampal cortices) and resection from one or more of the olfactory regions (piriform cortex, amygdala). As both surgical approaches involved the olfactory regions of interest, and due to the small number of SAH subjects, (which would limit the statistical power of an analysis), SAH and CAH patients were

combined, and patients were assigned to two groups based on the side of resection: left resection (LR) and right resection (RR).

Table 2. MRI scan measurements: Extent of tissue remaining in surgical hemisphere

| Region of surgical resection* | Left residual n = 10 Mean (*range*) | Right residual n = 11 Mean (*range*) | Measures of *intact* structures† Mean (*range*) |
|---|---|---|---|
| Hippocampus | 27mm (16-39) | 21mm (8-38) | 35mm (17-40) |
| Entorhinal cortex | 7mm (0-15) | 4mm (0-10) | 26mm (23-30) |
| Parahippocampal cortex | 19mm (16-25) | 15mm (3-21) | 22mm (16-27) |
| Piriform cortex | 36% (0%-78%) | 34% (0%-100%) | |
| Amygdala | 19% (0%-33%) | 14% (0%-33%) | |

*Measurements of structures in the surgical hemisphere: left temporal structures in LR patients and right temporal structures in RR patients. Amygdala and piriform are presented as percentages of intact tissue (see text).

†Measurements of intact structures in the unoperated hemisphere are provided for comparison.

Stimulus Materials

Odorants were provided by the Givaudan-Roure Corporation (Teaneck, New Jersey). All odors were presented dirhinally via puffs of scented air, presented approximately 1 inch below the nose, from opaque squeeze bottles in a format modified from Cain, Cometto-Muñiz and de Wijk (1992). Forty-eight odors arising from 12 veridical categories (four from each category) were used (Table 3). In order to reduce the effectiveness of verbal labels, foil odors for recognition testing were chosen from the

Table 3. Olfactory Stimuli

| Odor categories | Target odors | Foil odor sets | | | | | |
|---|---|---|---|---|---|---|---|
| | | Set A1 | | Set A2 | | Set A3 | |
| Citrus | Grapefruit | Lime Oil | 85% | Bergamot | 90% | Orange Oil | 76% |
| Fruity | Peach | Allyl Caproate | 76% | Guave | 85% | Amyl Acetate | 86% |
| Woody | Patchouly | Sandalwood Oil | 71% | Vetyver | 71% | Mousse de Chêne | 70% |
| Balsalm oils | Hydrocarboresin | Peru Balsam | 95% | Labdanum Oil | 90% | Fir Balsam | 86% |
| Grassy | Cis-3-hexanol | Galbanum | 80% | Lentisque | 90% | Viridine | 80% |
| Minty | Eucalyptus oil | Peppermint Oil | 90% | L-Carvone | 90% | Wintergreen | 85% |
| Spice | Cinnamon Bark Oil | Nutmeg Oil | 85% | Ginger Oil | 95% | Pepper Oil | 85% |
| Anise | Anisic Aldehyde | Fennel Oil | 85% | Star Anise Oil | 90% | Tarragon Oil | 90% |
| Light Floral | Geraniol | Muguet | 80% | Lilial | 90% | Freesia | 86% |
| Heavy Floral | Mimosa | Jonquille | 95% | Narcisse | 80% | Jasmine | 76% |
| Animal like | Indole Pure | Ambrarome | 90% | Castoreum | 90% | Civet | 76% |
| Unpleasant | Costus Oil | 2-Methyl Butyric Acid | 80% | Isovaleric Acid | 95% | Butyric Acid | 80% |
| Mean discrimination between target and foil odors*: | | | 84% | | 88% | | 81% |

*Percentages are percent correct discrimination between target and foil odors during pilot testing (see text)

same categories as the target items. For example, if a subject labelled a target odor as "fruity", this would be ineffective, because a "fruity" foil odor would occur during recognition. In order to ensure that subjects could discriminate among odors arising from the same category, and among odors from a similar category, pilot testing for odor discriminability was carried out. The odors were divided into six comparison sets, each consisting of two similar categories: fruity/citrus, woody/balsam-wood, heavy-floral/light-floral, minty/grassy, spice/anise, animal-like/unpleasant. Six groups of 20 healthy control subjects (60 men and 60 women in total) participated in the discrimination tests. A three-choice oddball paradigm was used, with dirhinal odor presentation; subjects stated which odor was the different one. Based on the results of the pilot study, the most highly discriminable odor from same-category odors and close-category odors was selected to be a target odor in the memory experiement. This resulted in twelve target odors for the memory test, one from each of the odor categories. The mean percent correct discrimination of all the target odors from their respective veridical *and* ecologically-close odors was 85% (range = 70% – 95%; median = 85%; mode = 90%). The three foil odors from each category were randomly distributed across three recognition-trial odor sets (A1, A2, A3). Three testing forms were created such that, across forms, each recognition-set was used at each of the different testing intervals (first recognition, second recognition, and 24hr delay). Use of the different test forms was counterbalanced across subjects.

Procedure

All subjects were screened for normal odor detection thresholds using a modified monorhinal two alternative forced-choice detection of phenylethyl alcohol (PEA) versus

water. Subjects passed this screening if they were able to correctly detect the PEA on four consecutive trials.

For the odor memory test, during the encoding phase, the twelve target odors were presented serially with a 20-second interstimulus interval. Subjects were told to smell the odor and try to remember it. They were advised that they would never be asked to name an odor. Three minutes after the last target was presented, subjects underwent the single exposure recognition trial (SER) with presentation of 24 odorants: the 12 target odors interspersed amongst 12 new odors. Subjects gave a "yes/no" recognition response for each item. This was followed by three subsequent presentations of the target odors, for learning, and then the fourth exposure recognition trial (FER) using 12 new foil odors. Subjects then returned the next day for a 24-hr delayed recognition test, with the 12 target odors interspersed amongst the third set of foil odors. Scores were obtained by adding correct hits (max=12) and correct rejections (max=12) for a total possible score of 24 on each test.

## Results

A three-way repeated measures analysis with two between-group factors (group [LR, RR, NC] and sex) and one within-subjects factor (test: SER, FER, 24hr-delay) revealed a significant effect of group ($F_{2,55} = 10.2$, $p < 0.0002$) and test ($F_{2,110} = 22.4$, $p < 0.0001$). There was no effect of sex and there were no significant interactions. Post-hoc Tukey HSD tests for unequal N's revealed that the RR and LR groups were not significantly different from each other. However, both patient groups performed significantly worse than the normal control group ($p<0.001$). A post-hoc Tukey test of the main effect of trial showed that performance on the FER trial was significantly better

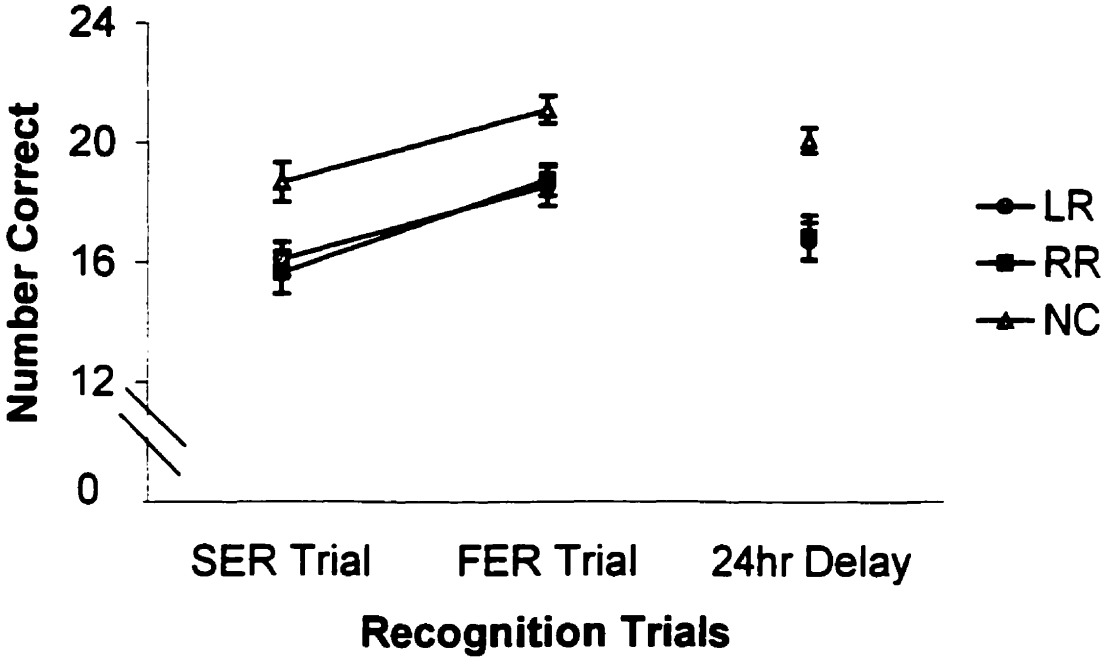



Figure 1

Odor recognition memory scores: group X recognition test, showing mean number of odors correctly identified as odors smelled previously, or as new odors. Three recognition tests: the single exposure recognition trial (SER) following the first presentation of 12 target odors, the fourth exposure recognition trial (FER) after three additional presentations of the target odors, and a final memory test following a 24hr delay interval. LR = Left resection, n=21; RR = Right resection, n=19; NC = Normal control, n=21.

than performance on the SER trial ($p<0.001$) and performance after a 24-hour delay ($p<0.001$). Recognition memory after a 24-hour delay was significantly better than recognition on the SER trial ($p<0.006$) (Figure 1).

Discussion of olfactory memory in patients with resection from a temporal lobe

In accordance with a number of the previously mentioned olfactory memory studies (Eskenazi et al., 1986; Martinez et al., 1993; Rausch et al., 1977; Savic et al., 1997), no significant differences were noted between patient groups as a function of side of temporal lobe resection. In fact, the similarity of the performance across trials for these two groups was striking, and both were impaired compared to healthy control subjects. There was no significant interaction of group by trials, indicating that the pattern of performance across the three trials was the same for the three groups. Performance of the LR and RR groups on the Single Exposure trial was at 67% correct, while the NC group performed at 79% correct, with little information lost from the Fourth Exposure trial to 24 hour delayed recall (NC group lost 4%, left and right groups lost 8%). The results for the long-term retention are in keeping with the findings of Engen and Ross (1973) and Lawless and Cain (1975), which showed imperfect initial recall after a single exposure (70-85% recognition immediately after all odors were presented) with a forgetting curve that did not exceed a 10% loss of information even after a 30 day delay [See Schab and Crowder (1995) for review].

Initial odor encoding in the patient groups was poor, and although they were able to learn with additional exposures, they were not able to recover from this initial deficit. One possible explanation for their poor performance is that they were impaired in

discriminating among the different odors presented. Discrimination deficits have been noted in patients with temporal-lobe lesions; however these deficits are relatively mild and are restricted to the nostril ipsilateral to the side of lesion (Zatorre & Jones-Gotman, 1991). Therefore, employing a dirhinal paradigm combined with the use of odors that have been tested for their high discriminability should lead to adequate discrimination performance for this type of recognition test. Indeed, if these patients did have some difficulties in discrimination it did not impair their ability to learn the odors, as their learning curve closely mirrored the performance of the healthy control subjects.

The issue of verbal labelling was also addressed in the current paradigm. The question regarding the use of verbal labelling of odors is particularly important in lesion studies, as patients with a right hemisphere lesion may be able to ameliorate their performance by relying on their intact verbal skills. Hence, if right temporal lobe epilepsy patients are able to effectively apply a verbal strategy, this may contribute to the inconclusive findings across studies with regard to right hemisphere specialization. Although it is difficult to give accurate veridical labels for odors (Cain, 1979; Carroll et al., 1993; Lehrner et al., 1999b), a general category label may suffice as an additional memory cue. But in the current study the utility of applying general category labels was rendered much less effective. Therefore if the right temporal lobe is more involved in odor memory processing than the left, and if RR patients cannot compensate through labelling for losing this advantage (as in the present paradigm), one should see a greater disparity between the performance of LR and RR groups. However, this was not the case; both patient groups showed a clear and equal deficit, suggesting that both temporal lobes, perhaps specifically the piriform regions, play an important role in odor memory.

## Study II: Functional imaging of healthy volunteers

To gather converging evidence regarding the role of the piriform cortex in olfactory memory, and to gain additional understanding of other brain regions involved in olfactory memory, we used the functional imaging technique of positron emission tomography to study odor-memory processing in the healthy brain. By applying this complementary approach of studying brain function in subjects with resection from a temporal-lobe, and examining brain function in healthy subjects through imaging, a more comprehensive view can be taken that circumvents some of the limitations of either approach. For example, in patient studies, the area of brain lesion or resection typically involves a number of different anatomical structures (Jones-Gotman et al., 1997a; Trop et al., 1997), and the effects of disconnection between brain areas are unclear. Thus, although it is possible to learn what broad brain regions are necessary to perform a particular task, this approach does not allow examination of the function of specific brain structures within and outside that brain region. On the other hand, brain imaging can give us more specific information about the different structures that may be involved in olfactory recognition, as well as insight into differences in functional participation of a particular region across a range of cognitive processes (e.g. encoding, short-term and long-term recognition). By melding these two approaches, it is possible to investigate the performance of brain regions during different odor memory processes, and to learn what regions need to be intact in order to recognize odors without impairment.

Subjects were scanned while performing a similar task to that of Study I. Three odor processing scans were performed: odor encoding, short-term recognition, and long-

term recognition. Subjects were also scanned during a no-odorant baseline condition, which acted as a control for motor movements and air sensations against the face. By subtracting the regions of brain activity occurring during this baseline condition from each of the three odor processing scans we were able to examine the brain regions involved specifically in odor encoding and recognition. In order to compare differences in activity that may occur between short- and long-term recognition, the two PET rCBF recognition-images were subtracted from each other. Predicted areas of activity during odor processing included: bilateral piriform and right orbitofrontal cortices (related to odor processing), temporal lobe activity(related to memory components), and differential activity in left and right prefrontal areas (related to encoding and/or recognition processes) (Buckner, 1996; Tulving et al., 1994; Wagner et al., 1998).

## Method

### Subjects

Twelve healthy right-handed volunteers (6 men, 6 women) participated in this study (mean age = 24.8; range = 20 - 30 yrs). None had a previous history of neurological or psychiatric disorders. All subjects were non-smokers with no history of nasal injury. This study was approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital. Subjects were paid for their participation and gave informed written consent.

### Stimulus materials

Thirty-six of the 48 odors from study one were used in this experiment: the 12 target odors and 24 of the foil odors.

To equate for level of difficulty, the 12 target and 24 foil odors were assigned to two target-odor sets and four foil-odor sets such that mean discriminability scores were equivalent across recognition tests (Tables 4 and 5). Odors were presented dirhinally in puffs of air via opaque squeeze bottles. The baseline condition consisted of puffs of air without an odorant added (Figure 2). Odors were presented in the same way during the training session and during the PET scan: each odor was presented for approximately four seconds followed by a six-second interstimulus interval.

Procedure

Training session.

Subjects participated in a training session four days prior to the PET study, in order to learn the odors for the long-term odor recognition scan. Subjects were instructed to smell the six target odors and try to remember them. They were informed that they would never be asked to name the odors, and that they would just have to recognize the odors presented among others in a larger set. Subjects were also told to sniff with the same depth and frequency of inhalation throughout all tasks. Training consisted of an initial presentation of the six long-term target odors, a first recognition test (Recognition 1), then three serial presentations of the target odors as learning trials. A second recognition test (Recognition 2) followed the last presentation of targets (Figure 2). Recognition trials involved the pseudorandom presentation of the six target and six foil odors (Table 5). Yes-No recognition responses were given via key-press following each stimulus presentation.

Table 4. Training and long-term recognition odors for PET study

| Odor categories | Long-term Target odors | Training session: Recognition one — Foil set: One | | Training session: Recognition two — Foil set: Two | | PET Long-term Recognition scan — Foil set: Three | |
|---|---|---|---|---|---|---|---|
| Citrus | Grapefruit | Orange oil | 76% | Lime oil | 85% | Bergamont | 90% |
| Heavy floral | Mimosa | Jasmin | 76% | Narcisse | 80% | Jonquille | 95% |
| Grassy | Cis-3-Hexanol | Lentisque | 90% | Galbanum | 80% | Viridin | 70% |
| Animal like | Indole | Ambrarome | 90% | Civet | 77% | Castoreum | 90% |
| Balsam oils | Hydrocarboresin | Labdanum | 90% | Peru Balsam | 95% | Fir Balsam | 86% |
| Anise | Anisic aldehyde | Tarragon | 85% | Star Anise | 90% | Fennel | 75% |
| Mean discrimination between target and foil odors*: | | | 85% | | 85% | | 84% |

*Percentages are percent correct discrimination between target and foil odors during pilot testing (see text)

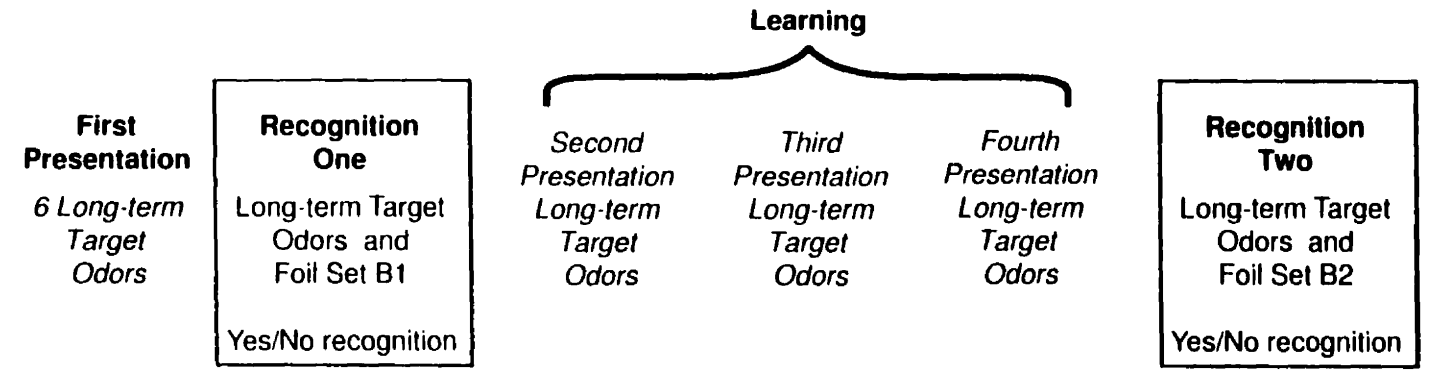
Table 5. Encoding and short-term recognition odors

| | Pet Scan Conditions | | |
|---|---|---|---|
| | Encoding | Short-term Recognition | |
| Odor Categories | Short-term recognition Target odors | Short-term recognition Foil odors | |
| Fruity | Peach | Guave | 85% |
| Light floral | Geranol | Freesia | 85% |
| Minty | Eucalyptus | Wintergreen | 85% |
| Spice | Cinnamon oil | Nutmeg oil | 85% |
| Woody | Patchouly oil | Vetiver acetate | 71% |
| Unpleasant | Costus oil | Isovaleric acid | 95% |
| Mean discrimination between target and foil odors*: | | | 84% |

*Percentages are percent correct discrimination between target and foil odors during pilot testing (see text)

Figure 2. Paradigm for Training and PET sessions

## Training Session




## PET Session: Four Days After Training

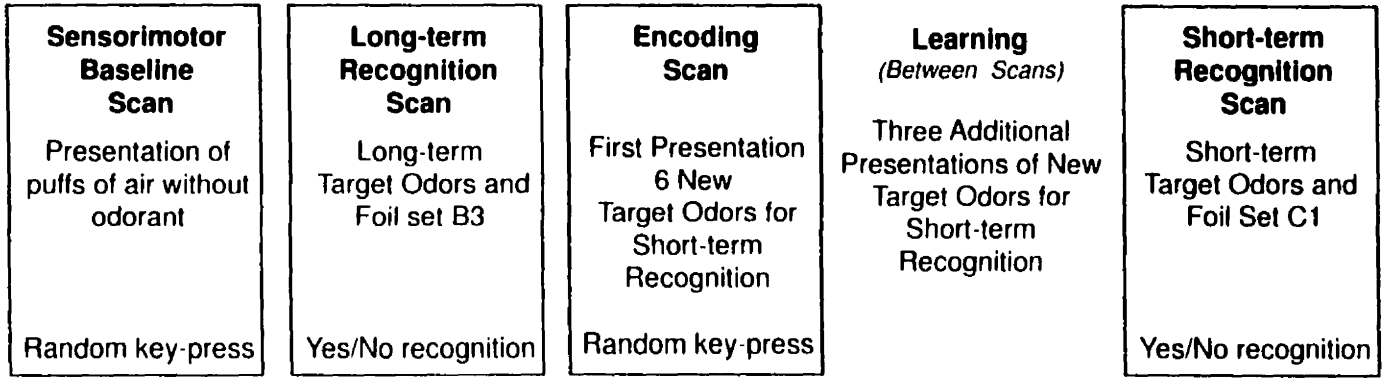



Figure 2
Schematic representation of the PET study paradigm

PET.

Subjects returned four days following the training session and were scanned during four conditions: (1) No-odorant sensorimotor control task, (2) long-term odor recognition, (3) encoding of new odors, and (4) short-term odor recognition. All scans occurred in the same order and included six odor presentations, at the rate of one odor each ten seconds, over the 60-second scanning period. Each recognition task consisted of twelve stimulus presentations: six presentations occurred during scanning, with four to five of the *target* stimuli presented (and one or two foil stimuli) during the PET data acquisition window to ensure that the results would reflect potential odor recognition. Yes-No responses were given via key-press. Subjects were reminded to sniff in the same way throughout all scans including the baseline control-task and to keep their eyes closed during each condition. Prior to the no-odorant control task, subjects were informed that they would feel the puffs of air, but that no odorant would be present. In this condition subjects made random key-press responses following each air-puff presentation to control for motor function. The six odors presented during the encoding scan were used as the target odors for the short-term recognition scan (Table 5). Between the encoding and short-term recognition scans, the short-term target odors were presented serially three additional times, to approximate the number of odor exposures subjects had experienced with the long-term target odors prior to recognition (Figure 2).

Data acquisition and analysis

PET scans were obtained using a CTI/Siemens HR+ 63 slice tomograph with an intrinsic resolution of 4.2mm x 4.2mm x 4.2 mm. Regional cerebral blood flow (rCBF) was measured during a 60- second scan using the $^{15}O$ water bolus method (Raichle,

Martin, Herscovitch, Mintum, & Markham, 1983). Magnetic resonance imaging scans were obtained using either a Siemens Vision (1.5T) or a Philips ACS III (1.5T) scanner. Both produced a high-resolution 3D whole brain T1 weighted scan (~ 140-160 1mm sagittal slices). PET and MRI scans were co-registered and resampled into standardized stereotaxic space (Evans et al., 1992; Talairach & Tournoux, 1988). Images were reconstructed using a 14-mm Hanning filter and averaged across subjects for each scanning condition. Differences in rCBF were examined by doing a paired image subtraction of scans of interest. The significance of focal CBF changes was evaluated using a method based on three-dimensional Gaussian random field theory (Worsley, Evans, Marrett, & Neelin, 1992). A threshold for significant *t*-statistic peaks was set at $t \geq \pm 3.53$ ($p \leq 0.0004$) for grey matter volume of 500 $cm^3$ and 182 resolution elements (14x14x14 mm), yielding a false-positive rate of 0.58. For the principal olfactory regions (piriform cortex and right orbitofrontal cortex, insula), where activity was predicted based on previous findings (Zatorre et al., 1992), the threshold was lowered to $t = 3.0$. Locations were compared to the atlas of Talairach and Tournoux (1988) to assist in determining the anatomical correlates of the significant foci.

## Results

### Behavioral results

Subjects performed well on all recognition tests (mean percent correct during training:[Recognition 1 = 70%, Recognition 2 = 84%; mean percent correct during PET: Long-term delayed recognition = 76%, Short-term recognition = 85%). A one-way repeated measures analysis of variance for recognition tests one, two, and four-day

delayed recognition showed a significant difference in the percentage correct ($F_{2,22}$=6.53, $p< 0.01$). Post-Hoc Tukey tests revealed that performance on the fourth exposure trial, after learning, was significantly better than the single exposure recognition trial ($p<0.01$). Performance on the long-term recognition trial was not significantly different from trials one or two. A paired *t*-test comparing performance between the short- and long-term recognition PET tasks revealed significantly better performance on the short-term recognition task ($t_{11}$=1.76, $p = 0.05$; one-tailed).

PET results

Odor Encoding minus Baseline.

This subtraction was expected to reveal areas important for odor processing (piriform and orbitofrontal cortices) and perhaps greater left prefrontal activation activity related to encoding processes as proposed in the hemispheric encoding/retrieval asymmetry (HERA) model (Cabeza et al., 1997; Tulving et al., 1994). Unexpectedly, no significant activation was noted in primary (piriform) olfactory cortex. A region of sub-threshold activity was noted close to the right piriform ($t = 2.89$; $x = 21$, $y = 6$, $z = -11$), being near the average reported *x* and *y* Talairach coordinates (Talairach & Tournoux, 1988) of piriform activity calculated from four prior olfactory functional imaging experiments (Zatorre & Jones-Gotman, 2000). However, its location in the horizontal plane (*z* axis) was greater than three standard deviations dorsal to the average-*z* coordinate. The anomalous position of this activation, in addition to its low *t-value*, makes it difficult to interpret this finding. No significant activity was noted in the secondary (right orbitofrontal cortex) olfactory region. Significant activations were found only in bilateral superior ($t = 4.2$; BA 8; $x = 3$, $y = 27$, $z = 59$) and medial ($t = 4.0$;

BA 6; $x = 1$, $y = -14$, $z = 57$) frontal cortices, as well as in the left precentral gyrus ($t = 3.9$; BA 4; $x = -11$, $y = -32$, $z = 66$).

Long-term recognition minus Baseline.

Unlike the encoding condition, significant activity was noted in primary (bilateral piriform cortices) and secondary (right orbitofrontal) olfactory cortices as expected. These regions were close to the areas reported by (Small et al., 1997; Sobel et al., 1998; Zald & Pardo, 1997; Zatorre et al., 1992; Zatorre et al., 2000). Significant activity was also noted bilaterally in insular cortex.

Significant prefrontal activity was detected in bilateral cingulate regions (BA 32), an area detected in other encoding and retrieval studies (Buckner, 1996), and bilateral medial frontal (BA 8) cortex. Outside these areas of interest, activity was noted in right caudate, left precentral gyrus and right inferior parietal lobe. (Table 6 and Figure 3)

Short-term recognition minus Baseline.

Significant increased activity was present in bilateral piriform, right orbitofrontal (BA 11) and insular cortices during short-term recognition. This was interesting, as all except one odor used in this condition were the same as those presented during the encoding condition; only the cognitive demands had changed. Activity was also noted in dorsolateral prefrontal cortex, a region known to play a role in working memory (Goldman-Rakic, 1995; Petrides, 1994a; Petrides, 1994b).

Activity also occurred within bilateral pre and post central gyri and within the left lingual gyrus. (Table 6 and Figure 3)

Table 6

Numbers in parentheses refer to Brodmann areas. Brain regions are indicated by Talairach (1988) co-ordinates X, Y, and Z: *X* is the medial to lateral distance relative to midline (positive = right hemisphere), *Y* is the anterior to posterior distance relative to the anterior commissure (positive = anterior), *Z* is the superior to inferior distance relative to the anterior commissure-posterior commissure line (positive = superior).

Table 6. Recognition conditions minus the sensorimotor baseline control-task

| | Short-term recognition | | | | Long-term recognition | | | |
|---|---|---|---|---|---|---|---|---|
| **Location** | **X** | **Y** | **Z** | ***t* statistic** | **X** | **Y** | **Z** | ***t* statistic** |
| **Olfactory regions** | | | | | | | | |
| R piriform cortex | 28 | 10 | -21 | 3.0 | 23 | 3 | -14 | 4.7 |
| L piriform cortex | -23 | 1 | -14 | 3.6 | -20 | 5 | -17 | 3.9 |
| L insula | - | - | - | - | -28 | 15 | 17 | 3.8 |
| R insula | 34 | 20 | - 3 | 3.4 | 28 | 18 | 8 | 3.4 |
| R orbitofrontal (11) | 27 | 44 | -14 | 4.3 | 20 | 48 | -18 | 3.7 |
| R orbitofrontal (11) | - | - | - | - | 20 | 27 | -12 | 3.6 |
| **Prefrontal cortex** | | | | | | | | |
| R frontal polar (10) | 48 | 48 | - 5 | 4.6 | - | - | - | - |
| R mid-dorsolateral frontal (9/46) | 47 | 37 | 20 | 4.2 | - | - | - | - |
| Bilateral medial frontal (8) | - | - | - | - | - 1 | 22 | 51 | 3.9 |
| R medial frontal (8) | 8 | 29 | 39 | 5.5 | - | - | - | - |
| L cingulate (32) | - | - | - | - | -11 | 27 | 30 | 3.9 |
| R cinglate (32) | - | - | - | - | 11 | 39 | 23 | 3.5 |
| R superior frontal (6) | 26 | - 4 | 62 | 3.7 | - | - | - | - |
| **Motor/Sensory** | | | | | | | | |
| R caudate | - | - | - | - | 12 | 13 | - 5 | 3.7 |
| L precentral gyrus (4) | -30 | -23 | 59 | 3.9 | -28 | -21 | 50 | 3.8 |
| L pre/post central gyri (4 / 3) | -39 | -19 | 59 | 3.8 | - | - | - | - |
| R precentral gyrus (4) | 28 | -14 | 45 | 3.9 | - | - | - | - |
| R pre/post central gyri (4 / 3) | 35 | -25 | 53 | 3.6 | - | - | - | - |
| **Parietal Lobe** | | | | | | | | |
| R inferior parietal (7/40) | 40 | -57 | 48 | 5.5 | 43 | -56 | 48 | 3.6 |
| L inferior parietal (7/40) | -27 | -56 | 48 | 4.3 | - | - | - | - |
| **Occipital Lobe** | | | | | | | | |
| L lingual gyrus (18) | - 3 | -92 | -11 | 3.7 | - | - | - | - |

Figure 3

Brain sections were chosen to illustrate a majority of the relevant activations. Precise locations of the peaks for the activity shown are given in Table 6. The same right sagittal ($X = 44$), coronal ($Y = 5$), and horizontal ($Z = -16$) slices are shown for the long-term recognition minus the baseline control scan subtraction and the short-term recognition minus the baseline control scan subtraction. Long-term recognition = top three images. Short-term recognition = bottom three images. Numbers at activation sites represent Brodmann areas. PC = piriform cortex.

Long-term recognition minus Short-term recognition.

In the regions of interest, significantly greater activity was noted in right piriform cortex, left insula, and left mid-dorsolateral prefrontal cortex during long-term recognition. During short-term recognition, significantly greater activity was noted in left and right mid-dorsolateral frontal cortex, and the left frontal polar region. The differences in piriform and right mid-dorsolateral frontal activity between the two conditions can be noted in Figure 3, where the two tasks are compared to the same baseline condition. Additional regions of difference were found in parietal lobe and motor/sensory regions of the frontal lobe (see Table 7)

Relationship between PET results and extent of excision in patients

All patients had excision within at least one, and usually more than one, primary olfactory region (piriform cortex, amygdala, periamygdaloid and entorhinal cortices). Of patients who had MRI measurements, all but one had excision from the piriform cortex and all had excision from amygdala. To examine the relationship between the region of piriform activity detected during functional imaging and the region of temporal lobe resection in the patients, the long-term recognition PET data were coregistered in Talairach space (Collins et al., 1994; Talairach & Tournoux, 1988) with the structural MRI of a patient with a standard CAH resection. The area of odor recognition activity obtained in the healthy subjects overlaps, in part, with the excised temporal-lobe region, further indicating that important odor processing areas are invaded in the patient population. (Figure 4)

Table 7. Changes in CBF observed for the short-term minus long-term recognition subtraction

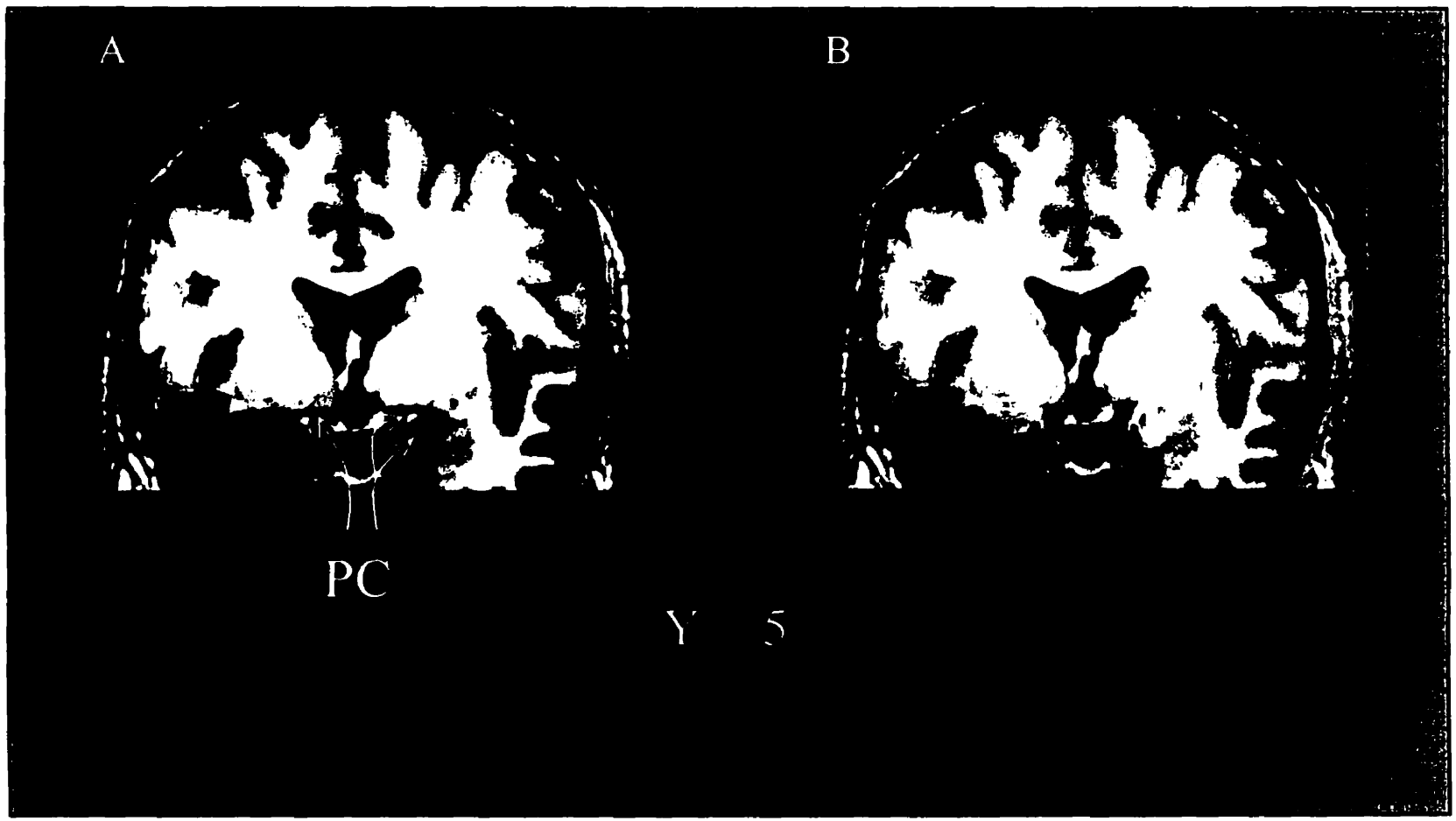
| Areas showing greater activity during the short-term condition | | | | |
|---|---|---|---|---|
| Location | X | Y | Z | *t* statistic |
| L frontal polar | -26 | 52 | 0 | 3.5 |
| R mid-dorsolateral frontal (9/46) | 30 | 44 | 8 | 3.5 |
| R superior frontal gyrus (8) | 11 | 24 | 48 | 3.7 |
| L mid-dorsolateral frontal (9) | -38 | 18 | 32 | 4.0 |
| R middle frontal gyrus (6) | 27 | - 2 | 60 | 4.5 |
| L precentral gyrus (4) | 26 | -19 | 52 | 5.2 |
| L superior parietal lobe (7/40) | -26 | -52 | 48 | 4.1 |
| R inferior parietal cortex (7/40) | 40 | -66 | 45 | 3.5 |

| Areas showing greater activity during the long-term condition | | | | |
|---|---|---|---|---|
| Location | X | Y | Z | *t* statistic |
| L mid-dorsolateral frontal (9/46) | -38 | 44 | 29 | 3.6 |
| L cingulate (32) | - 4 | 37 | - 2 | 3.6 |
| R medial frontal (11/25) | 5 | 15 | - 8 | 4.9 |
| L Insula | -34 | 6 | - 3 | 3.8 |
| R piriform cortex | 17 | 3 | -23 | 3.5 |
| L inferior parietal lobe (40) | -58 | -38 | 29 | 3.8 |

See table legend for Table 6

Figure 4

For the purpose of illustration the PET data from the healthy subjects have been superimposed on the MRI image of a representative left CAH patient (left hemisphere is on the left side in these images). Surgical resection invades the temporal portion of the left piriform region of PET activity, as obtained from healthy subjects. A) Coronal image of a patient MRI transformed into Talairach space (Y=5) [Talairach, 1988 #151]. B) Long-term recognition PET data coregistered to the patient MRI in stereotaxic space.


A
B
PC
Y 5

## General Discussion

The most interesting PET findings were the differences in piriform activation across the three odorant-processing conditions. The lack of piriform activity during encoding was notable, particularly considering that in the short-term recognition condition, where essentially the same odors were presented, piriform activity *was* observed in comparison to the same baseline condition. This modulation in piriform activity has been seen across different studies: The first $O^{15}$ PET study of human olfaction (Zatorre et al., 1992) showed strong bilateral piriform activity during smelling. However, a lack of increased piriform activity during smelling has been noted in other studies (Dade, Zatorre, Jones-Gotman, & Evans, 1997b; Sobel et al., 1998; Yousem et al., 1997; Zatorre & Jones-Gotman, 2000), and one study found only subthreshold changes that did not reach pre-set levels of significance (Zald & Pardo, 1997). Although increased piriform activity, related to smelling, was not consistently found in early fMRI studies (Sobel et al., 1998), this issue was resolved (Sobel et al., 2000b) by using a statistical approach that took into account the early transient increase in signal amplitude and response habituation that occurs in piriform regions when the same odor is presented repeatedly (Wilson, 1998a). Using this approach Sobel and colleagues (2000b) were able to consistently observe odorant-induced activity, in addition to sniffing activity (Sobel et al., 1998), in piriform and ventral temporal lobe regions.

The difficulties in fMRI analysis do not explain the differences in detection of piriform activity in the current study, as PET methodology is less susceptible to the error related to the transient increase in signal amplitude. PET allows one to examine the data

in a cumulative fashion, over a one minute scanning interval, rather than analyzing the data based on responses matched to the time course of stimulus presentation. Also the second factor of response habituation, due to subjects experiencing the same odor repeatedly during the same block (Sobel et al., 1998; Sobel et al., 2000b), would not apply to the current study. In one fMRI study, habituation was seen to occur after five presentations of the same odor (Sobel et al., 2000b), a result similar to that found in electrophysiological studies of rats (Wilson, 1998a; Wilson, 1998b). Findings from rat studies have also indicated that habituation in the piriform is odor specific (Wilson, 1998a). Therefore, it is probable that our paradigm, which consisted of the presentation of a series of *different* odors during each scan, would not cause habituation in piriform cortex, and our analysis would also not be susceptible to error due to this factor.

The possibility of differences in sniff-rate across the different conditions is also an important issue, as piriform activity is influenced by this behavior (Sobel et al., 1998; Sobel et al., 2000b). Although we were unable to measure sniff rate directly, subjects were told to always sniff in the same way (depth and rate of inhalation) for each condition (both in training and prior to each scan), regardless of the presence or absence of an odorant. Small differences (on the order of tenths of seconds) in sniff duration have been noted between presentation of low and high concentration odorants (Laing, 1983; Sobel, Khan, Hartley, Sullivan, & Gabrieli, 2000a); however all the odorants used in the present experiment were at suprathreshold detection levels, and there was no bias for lower concentration odorants in any one scanning condition (particularly between the encoding and short-term conditions where five of the six odors were the same). Given that subjects were sniffing during our baseline condition, that the pattern of stimulus

presentation was the same across all conditions, and that subjects were told to sniff in the same way during all scans, it does not appear that changes in rates of sniffing can adequately explain our findings.

Piriform cortex: A memory processor?

An intriguing finding is that in the same subjects, comparing to the same baseline scan, we have observed different levels of piriform activity in relation to the cognitive conditions of the task. Notably, the activation in piriform cortex appears to follow along a continuum between the encoding condition, with no significant activity present, to the short-term recognition condition with weak bilateral activity, to the long-term recognition condition, which shows strong bilateral piriform activity. Hence we see an increase in activity as a function of the recognition components of the task and perhaps in relation to odor familiarity. These findings are in agreement with the proposal of Haberly (Haberly, 1985; Haberly & Bower, 1989) and others (Bower, 1991; Hasselmo & Barkai, 1995), which suggests that the primary olfactory cortex serves as a type of associative memory system, which allows for the association of odor stimuli with memory traces of previously experienced scents.

Initially these inferences may not appear to be in accordance with the study by Zatorre et al. (1992), in which subjects were scanned during passive smelling of different odors, and strong bilateral piriform activity was noted. Nevertheless, there do appear to be factors that would contribute to a long-term memory processing aspect. Although the odors used in the Zatorre et al. (1992) study were difficult to name, most were common household products, and all were selected to be moderately to highly familiar. Also subjects were familiarized to the odors prior to the scanning condition. Perhaps due to

these two manipulations, when subjects smelled the familiar and recently smelled odors, activation of short- and long-term memory networks occurred within piriform regions.

Several findings lend support to the theory that piriform cortex is involved in learning and memory. First, synaptic long-term potentiation (LTP), which is known to be important in "hippocampal" memory (see Bliss and Collingridge, 1993, for review), has also been shown to occur in rat piriform cortex *in vitro* (Jung & Larson, 1994; Jung, Larson, & Lynch, 1990; Kanter & Haberly, 1990) and *in vivo* at the conclusion of learning (Litaudon, Mouly, Sullivan, Gervais, & Cattarelli, 1997; Roman, Chaillan, & Soumireu-Mourat, 1993). Interestingly, simple exposure to olfactory stimulation does not appear to be sufficient to effect change in piriform activity. For example, rat studies by Roman et al. (1993) and Litaudon et al. (1997) showed that alterations in piriform activity did not occur until the significance of the olfactory stimulation had been learned. Other evidence relating piriform cortex to memory function comes from the evaluation of single-neuron activity: different cells were detected which fired either in association to the physical characteristics of the odor, in association to the odor's reward value, or in association to its significance in relation to past events (Schoenbaum & Eichenbaum, 1995). Consequently, this evidence supports the concept that piriform cortex can serve a mnemonic function, as well as a perceptual one.

The findings of changes in piriform activity in rats *after* odor learning (Litaudon et al., 1997; Roman et al., 1993) may also explain the greater piriform activation during recognition than in encoding. Perhaps with multiple odor exposures, or "learning", larger responding networks were created, thus increasing cellular activity. Activity in piriform did not appear to increase with improved performance, as subjects performed better

during short-term recognition than long-term recognition. However, the greater piriform activity during long-term recognition could reflect increases related to memory consolidation processes. Memory consolidation, or the formation of long-term memories, is dependent on the passage of time and is theorized to be linked to the cellular mechanisms underling LTP (see (McGaugh, 2000) for review), which have been shown to occur in piriform cortices. The importance of piriform regions to memory performance was also supported by the patient findings in study one, as the resections in the patient groups encroached on piriform cortex, and the patients were equally impaired across all three recognition tests. Further, the combined findings from the patient study and the PET results of bilateral piriform participation during long-term recognition support the idea of an interactive role between left and right piriform regions in order to sustain normal odor recognition.

Odor recognition: a dual hemisphere task

Findings from patient studies showing deficits restricted to the nostril ipsilateral to the lesion (Eskenazi et al., 1986; Jones-Gotman et al., 1997a) and from studies with commissurotomized subjects (Gordon & Sperry, 1969), suggest that each hemisphere is independently able to perceive and recognize familiar odors. However, this does not preclude the existence of a more integrated and higher order cognitive system. In a study of odor recognition in healthy subjects, no differences were shown between the left and right nostrils, but dirhinal scores were significantly higher than monorhinal scores (Bromley & Doty, 1995). The superiority of dirhinal stimulation during an odor recognition task is consistent with findings for odor identification that showed mild

identification deficits after resection from either the left or right temporal lobe (Jones-Gotman & Zatorre, 1988).

Therefore, although evidence suggests that each hemisphere can function independently (Gordon & Sperry, 1969), it would appear that it is the interaction of the two that allows for optimal performance for more complex olfactory processing. One factor that may result in the improvement of function with bilateral participation is increased perceptual acuity, as described by Sobel, Khan, Saltman, Sullivan, & Gabrieli (1999), who showed that each nostril conveys different details about olfactory stimuli to the brain. Therefore it could be the case that slightly different olfactory percepts are encoded within each hemisphere, and it is some complex combination of information within the two piriform cortices that allows for more precise olfactory recognition.

Differences in short- and long-term recognition processing

In contrast to the strong piriform activity during long-term recognition, the short-term recognition condition showed greater activity in right mid-dorsolateral prefrontal cortex and parietal lobe, areas known to be important for working memory processing in the visual modality (Goldman-Rakic, 1995; Petrides, 1994a; Petrides, 1994b). These same regions have been shown to be active during functional imaging of an olfactory working memory task (Dade et al., 1997b). Hence these results demonstrate a differentiation between short- and long-term memory processing, and suggest that short-term recognition tasks and working-memory tasks (requiring information monitoring and manipulation) engage some of the same anatomical regions.

Insular participation

Insular activity was detected unilaterally on the right during short-term recognition and bilaterally in the long-term recognition condition. The insula is known to receive axonal projections from primary and secondary olfactory regions (Price, 1990; Price et al., 1991), and similar insular and peri-insular activity has been detected during other olfactory functional imaging studies (Fulbright et al., 1998; Sobel et al., 1998; Zald & Pardo, 1997; Zatorre et al., 1992). The insula is thought to be important for gustation (Shipley & Ennis, 1996; Small et al., 1997; Small et al., 1999), and activation during this olfactory task may be reflective of the olfactory role in flavor perception.

Orbitofrontal regions

A very consistent finding in the olfactory imaging literature [see Zald and Pardo (2000), and Zatorre and Jones-Gotman (2000) for review], and in the recognition conditions of the current study, is the unilateral right orbitofrontal activity. The orbitofrontal region observed in the short- and long-term recognition conditions corresponds most closely with the lateral posterior orbital cortex identified in the monkey (Tanabe, Yarita, Iino, Ooshima, & Takagi, 1975b). Cells in this region were found to respond more selectively to different odors than cells in either the piriform or amygdala regions (Tanabe, Iino, & Takagi, 1975a), and findings from this animal study, and from studies of patients with orbitofrontal lesions (Potter & Butters, 1980; Zatorre & Jones-Gotman, 1991), suggest that the orbitofrontal region plays an important role in odor discrimination.

However it is curious that, as with the piriform region, no orbitofrontal activity was noted during the encoding condition. The presence of orbitofrontal activity during

recognition, and the lack of significant activity during encoding, may be related to the greater odor-discrimination demands required during recognition (discriminating between serially presented target and foil odors), that are not requisite during initial encoding. Also the episodic memory component of recognition introduces an additional factor. For example, Royet et al. (1999) found greater right orbitofrontal activity when subjects had to make judgments about the familiarity of odors versus judgments of edibility (which would not necessarily involve episodic memory), suggesting a possible long-term odor recognition component to the functioning of the right orbitofrontal region. Further investigation is necessary, using more closely controlled comparisons that require equivalent levels of discrimination in order to tease apart activity due to increased discrimination demands (e.g. choosing between closely matched odors) versus increased demands of retrieval (e.g. long delay intervals).

Prefrontal cortical involvement

Activity in prefrontal cortex also needs to be considered in terms of processing demands. The hemispheric encoding\retrieval asymmetry model (HERA) broadly suggests that left prefrontal cortex is differentially involved in encoding, while right prefrontal cortex was differentially involved in retrieval (Tulving et al., 1994). A limitation of this model is that it does not describe particular anatomical regions within prefrontal cortex that perform these functions. In a more detailed analysis, specific prefrontal regions involved in encoding (left inferior frontal BA 44 and BA 45 during verbal encoding) and retrieval (right anterior frontal BA 10) were identified (Buckner, 1996). In the current study the most prominent source of prefrontal activity is within the right orbitofrontal region during recognition. Thus, it would seem that orbitofrontal

activity (BA 11) is not usually present in studies of information retrieval and, in the current paradigm, its function is directly related to the *olfactory* recognition demands of the task. Findings of significant increases in blood flow in right BA 10 and right BA 9/46 during the short-term odor recognition condition do fit with the above model, and also with activity detected during an olfactory working memory task (Dade et al., 1997b). However, these same regions are not active during long-term odor recognition, which suggests that working memory areas can be engaged during short-term memory processing, but that these regions are not relied on during long-term memory retrieval.

## Conclusion

When using an odor recognition paradigm that controlled for the confound of verbal labelling, no hemispheric superiority was found among patients with resection from the left or right temporal lobe regions. These findings combined with imaging data from healthy subjects support a dual hemisphere role in odor memory processing. In concert with findings from animal studies (Litaudon et al., 1997; Roman et al., 1993), our findings suggest that the role of the piriform cortex extends beyond 'simple' sensory processing and reaches into the realm of memory function.

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## Connecting text

In the olfactory memory study, patients with resection from the left or right temporal lobe were impaired across all three recognition tests for this nonverbal stimulus. These results combined with the PET findings supported a role for dual hemisphere processing for this type of nonverbal information and this experimental paradigm. In the following study, learning and memory for faces was investigated, to examine further how the left and right temporal lobe regions process and retain nonverbal information. By using a similar testing paradigm and the same type of patient groups (LR and RR), I was able to determine any similarities and differences that occur on learning and retention for the two types of nonverbal stimuli (odors and faces).

## Chapter Three

# Face learning and recognition:

# A new paradigm to examine right hemisphere function

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Abstract

Impaired face recognition has been demonstrated in patients with right temporal-lobe lesions. The current study examined face memory more extensively by testing learning and retention using a novel paradigm. Recognition was tested on three trials: after a single exposure, after four exposures (for learning), and following a 24hr delay interval. Patients with resection from the right temporal lobe performed significantly worse than healthy control subjects and patients with resection from the left temporal lobe. There was no difference in performance between patients with resection from the left temporal lobe and healthy control subjects. The ability of the test to classify individual patients correctly to side of temporal lobe resection was examined: sensitivity was 82% and specificity was 79%. The contribution of different temporal lobe structures to face memory is discussed, and issues regarding memory assessment are raised.

Early studies of face recognition in patients with brain lesions indicated that face perception and memory relied predominantly on right-hemisphere brain structures (Benton & Van Allen, 1968; De Renzi & Spinnler, 1966, Milner, 1968; Warrington & James, 1967). Recent structural imaging studies of prosopagnosic patients (impaired in face perception and/or recognition) have also given more support to the argument that this disorder is strictly related to right hemisphere damage (De Renzi, Perani, Carlesimo, Silveri, & Fazio, 1994; Takahashi, Kawamura, Hirayama, Shiota, & Isono, 1995). Right hemisphere superiority for face processing has also been noted in tachistoscopic studies of healthy subjects, showing a left visual field (LVF) dominance (indicative of right hemisphere processing) for face recognition (see Rhodes, 1985, for review). This is further supported by research on viewer preference for the right hemiface (Gilbert & Bakan, 1973; Kolb, Milner, & Taylor, 1983). In studies of hemiface preference, subjects reliably judged composite photos, made up of the right side of a face and its mirror-image, as being more like the original faces than left hemiface composite images (Kolb et al., 1983). This right hemiface preference, which is also a LVF preference, is again though to reflect the facility of the right hemisphere in face processing.

More recently, the functional lateralization of face processing has been supported by Positron Emission Tomography (PET) (Haxby et al., 1994; Kuskowski & Pardo, 1999; Sergent, Ohta, & MacDonald, 1992) and functional Magnetic Resonance Imaging (fMRI) studies (Haxby, Hoffman, & Gobbini, 2000; Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Gore, & Allison, 1997; Puce, Allison, Asgari, Gore, & McCarthy, 1996). Findings from these and other studies have led to the demarcation of a region in

extrastriate cortex called the fusiform face area (FFA), which increases in activity when subjects are viewing faces (Allison et al., 1994; Gauthier, Tarr, Anderson, Skudlarski, & Gore, 1999; Haxby et al., 1994; Kanwisher et al., 1997; McCarthy et al., 1997). Across subjects, increased activity has been shown most consistently in the right as opposed to the left FFA when looking at faces (Kanwisher et al., 1997). Interestingly, the preferential engagement of the right hemisphere for face processing is not restricted to humans. This phenomenon has also been recently reported to occur in sheep via behavioral studies using hemifield and chimeric sheep faces as stimuli (Peirce, Leigh, & Kendrick, 2000), and through examination of in-situ c-*fos* mRNA expression in relationship to sheep face exposure (Broad, Mimmack, & Kendrick, 2000).

Although there is a great deal of evidence for right hemisphere superiority in face processing, G. Rhodes (1985) is very clear in reminding researchers that "...an asymmetry [of function] favoring one hemisphere does not imply a complete lack of competence by the other hemisphere". For example, Levy et al (Levy, Trevarthen, & Sperry, 1972), using a tachistoscope, showed chimeric faces to patients who had undergone cerebral commisurotomy for the treatment of epilepsy. When these patients were asked to pick the face they had seen out of an array, all showed a preference for the face represented on the left side of the chimeric image, indicating right hemisphere superiority for the task. However, when subjects were required to make a naming response, the hemispheric-superiority shifted to the left hemisphere as demonstrated by the subjects responding more frequently to the right side of the chimeric face. Models of face recognition (Bruce, 1983; Rhodes, 1985) suggest a role of the left hemisphere in processing semantic information that relates to faces, such as names, as well as physical

and social attributes. Thus the role of the left hemisphere is often linked to recognition of highly familiar and/or famous faces (Farah, 1996; Tempini et al., 1998; Leveroni et al., 2000; Rhodes, 1985), and less to the recognition of previously unfamiliar faces. Evidence from prosopagnosic patients also lends support to the idea that recognition of familiar versus recently viewed unfamiliar faces depends on slightly different neurological substrates, as some prosopagnosic patients show greater deficits for familiar faces, while there are some patients who show greater deficits for unfamiliar faces (Farah, 1996).

Consequently, although the left hemisphere may play a role in some types of face recognition, learning and recognition of previously unfamiliar faces appear to rely heavily upon the right hemisphere, and more specifically on right temporal lobe regions (Haxby et al., 2000; Kanwisher et al., 1997; Takahashi et al., 1995). However, despite this close association between right hemisphere function and face recognition, there are only a small number of neuropsychological tests that examine recognition for previously unfamiliar faces (Benton & Van Allen, 1968; Denman, 1984; Milner, 1968; Warrington, 1984), and none that examine face learning and long-term retention.

In addition, the clinical utility of the few tests that examine recognition for previously unfamiliar faces has been questioned. The Warrington Recognition Memory Test (WRMT) (Warrington, 1984) compares memory performance for visually presented words to memory performance for unfamiliar faces. In the validation study of patients with unilateral cerebral lesions (the majority being of neoplastic or vascular pathology), patients with left hemisphere lesions had significantly worse performance on the words than the faces, while patients with right hemisphere lesions exhibited the opposite profile

(Warrington, 1984). A similar finding occurred in patients with unilateral excisions from a temporal lobe. But in this instance the face recognition test was shown to be more sensitive in detecting right temporal lobe lesions than the word recognition test in determining left temporal lobe lesions (Baxendale, 1997; Morris, Abrahams, & Polkey, 1995). Although face tests appear to classify patients with distinct brain lesions correctly, classification of patients with less well delineated brain disturbance, such as in unoperated patients with epilepsy, has had mixed levels of success. Preoperative studies of epilepsy patients' performance on the WRMT showed poor classification sensitivity and specificity for left and right temporal-lobe epilepsy patients (Hermann, Connell, Barr, & Wyler, 1995; Kneebone, Chelune, & Luders, 1997; Naugle, Chelune, Schuster, Lüders, & Comair, 1994). A study using the Denman Face Recognition test showed a significant difference between left and right temporal-lobe epilepsy patient groups (Barr, 1997). However, the small difference between the mean group scores raises questions about its utility in individual classification.

The findings of these clinically focused face recognition studies have raised issues about the utility of face memory tests in the detection of right hemisphere dysfunction within an individual. But evidence continues to support the potential usefulness of face tests in assessing right hemisphere function (Cahn et al., 1998), and research in this area is propelled onward by the relative paucity of effective neuropsychological tools to assess right hemisphere dysfunction (Barr, 1997; Jones-Gotman, Smith, & Zatorre, 1993) as compared to tools to assess dysfunction in the left.

However, creating a face recognition test has particular challenges due to the ease with which healthy subjects are able to recognize a large number of faces with only a

single exposure. Data from the WRMT shows that healthy individuals have a facility for recognizing faces; in the validation sample of 310 subjects, the mean face recognition scores for each five year age group (from 25 to 70 years of age) ranged between 42.3 and 44.8 out of a total possible score of 50 (Warrington, 1984). This proficiency in recognition makes it difficult to create a test of sufficient difficulty to assess learning, as healthy subjects make minimal recognition errors following one presentation, leaving little room to show improvements. For the Milner (Milner, 1968) and highly similar Denman (Denman, 1984) face tests, the faces to be recognized are presented in a single array for a one-time exposure. This may increase the difficulty of the task, but other issues arise with this procedure. For example, subjects may not look at the faces for the same proportion of time, or they may not even look at *all* the faces before the viewing time is over. Therefore, some subjects may not perform well due to a disorganized approach to viewing the faces, rather than due to impaired face recognition.

The WRMT involves a single presentation of 50 faces in a serial fashion, with each face being shown for 3 seconds. This form of presentation ensures that subjects see all the items, and that they spend the same amount of time viewing each one. However, assessment of memory after only a single learning trial also has difficulties. Patients may perform poorly due to decreased attention during that one trial, or due to incomplete comprehension of the nuances of the task, which may only become clear after that one trial is over. Testing subjects a second (or third) time, following several learning trials, allows the examiner to determine if poor performance on the initial trial was due to one of these secondary factors, or due to an actual impairment in learning the materials. A more powerful form of assessment arises from combining tests of learning with tests of

long-term retention. Jones-Gotman and colleagues (Jones-Gotman et al., 1997; Jones-Gotman, 1996; Majdan, Sziklas, & Jones-Gotman, 1996) have suggested that there are differences not only in preference for types of memory material that the left and right temporal lobes process, but also in how they process it. Dysfunction in left temporal lobe processing leads only sometimes to slower learning, and always to more rapid forgetting, of verbal material, while dysfunction in the right temporal lobe results in impaired learning of abstract designs, but little forgetting of the material over time. Thus, information about how well the material was learned and retained can help in issues of lateralization.

The focus of the current study was to investigate face memory more extensively: 1) by examining face configuration learning and long-term retention (24hrs), two areas that have not been assessed previously; and 2) by assessing the role of the temporal lobes by comparing the performance of healthy control subjects to that of patients with resection from the left or right temporal lobe. Pilot testing confirmed that healthy subjects could recognize a large number of faces very easily after a single exposure, leaving little room for learning to occur. Thus, in order to increase the difficulty and specificity of the task, sets of faces that differed only in the configuration of the facial features were created. Using this test we were able to examine recognition after a single exposure to the target faces, recognition after four exposures, and retention after a 24hr-delay interval. Based on the hypotheses of Jones Gotman and colleagues (Jones-Gotman et al., 1997; Majdan et al., 1996), we predicted that patients with a left resection would learn and remember faces adequately. In contrast, we predicted that patients with a right resection would show poor learning, but what they learned would be maintained over a 24hr period, thus revealing the same pattern of deficits as observed in patients with left

or right temporal lobe deficits when learning and remembering other nonverbal material (abstract designs) (Jones-Gotman, 1986; Jones-Gotman, 1996; Jones-Gotman et al., 1997; Majdan et al., 1996). The clinical utility of this testing paradigm will also be evaluated by examining the specificity and sensitivity measures for classification of individual patients to left or right resection groups.

## Method

### Subjects

Seventy-two subjects participated in this study: thirty–six patients who had undergone resection from either the left (LR, n = 19) or right (RR, n=17) temporal lobe for the treatment of intractable epilepsy, and thirty-six healthy control subjects (NC) approximately matched to patients for age and years of education (Table 1). All patients in this study had undergone a preoperative evaluation including EEG, magnetic resonance imaging (MRI), and clinical examination that had localized their seizure origin to a single focus. All except for three patients were right handed. Left-handed patients were shown to have left hemisphere speech as determined by preoperative intracarotid amobarbital testing (Branch, Milner, & Rasmussen, 1964). Patients were of normal intelligence with Full-Scale WAIS-R IQ ratings above 80 (Wechsler, 1981). Analysis of variance did not reveal any significant difference in IQ ratings between the two patient groups, and there were no significant differences in age or education among the three groups. This study was approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital, and all subjects gave informed written consent.

Table 1. Subjects

| Group | *n* | Mean age *(range)* | Mean years of education *(range)* | Mean IQ *(range)* |
|---|---|---|---|---|
| LR | 19 | 33.5 (22-43) | 14.1 (10-20) | 102.3 (84-135) |
| RR | 17 | 35.9 (22-51) | 14.2 (10-21) | 99.1 (84-120) |
| NC | 36 | 36.3 (21-61) | 13.9 (10-18) | - |

LR = left resection
RR = right resection
NC = normal control

Patients had undergone one of two different surgical approaches. Eleven (5 left, 6 right) of the 36 patients had undergone a selective amygdalohippocampectomy (SAH). This surgical procedure involves making a small 2 to 3-cm incision through the second temporal gyrus, just beneath the superior temporal sulcus. The sulcus is followed to the floor of the lateral ventricle, where 0.5 to 2.5 cm of hippocampus, and partial to complete resection of the amygdala occurs. In this procedure the cortex remains relatively intact (Trop, Olivier, Dubeau, & Jones-Gotman, 1997). The remaining 25 patients underwent a corticoamygdalohippocampectomy (LR = 13; RR = 12). This approach consists of a cortical removal extending 4.5 to 5.0 cm along the Sylvian fissure, continuing to the level of the precentral sulcus with partial to complete removal of the amygdala, and excision of approximately 0.5 to 3 cm of the hippocampus and parahippocampal gyrus (Trop et al., 1997). The SAH and CAH groups are similar in their extent of resection from mesial temporal lobe structures. In the region of the fusiform gyrus, SAH patients do not typically have any resection, but a small portion may be resected in CAH patients. Kanwisher and colleagues (Kanwisher et al., 1997) found significant activation of fusiform structures in left ventral cortex at approximately -35x, -63y, -10z and in the right hemisphere at approximately 40x, -55y, -10z in Talairach space (Talairach & Tournoux, 1988). Similar sites of activity were also noted during a PET study examining face recognition while utilizing the same stimuli as in the current study (Dade, Zatorre, Jones-Gotman, & Evans, 1997). Although only a few of the subjects in the current study had postoperative MRIs available for measurement of the area of surgical resection, information about the usual extent of removal in lateral temporal cortex is available from another study within this institute (Crane, 1999). In this study, the extent of resection of

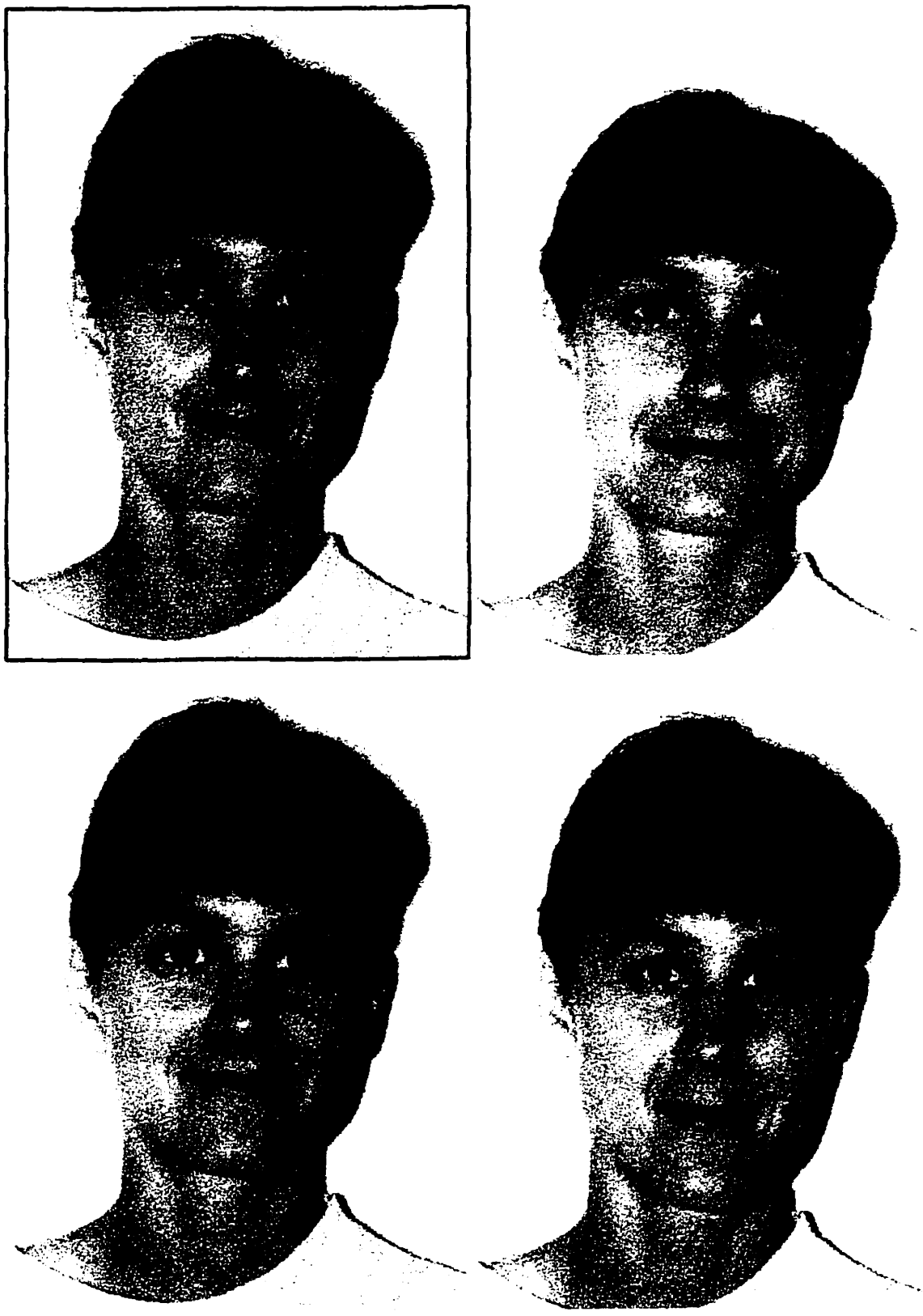
temporal lobe structures was measured in a large sample of 45 CAH patients (21 right CAH, 24 left CAH) via postoperative MRI (Crane, 1999). Each scan was transformed into Talairach space (Talairach & Tournoux, 1988) using an automated algorithm (Collins, Holmes, Peters, & Evans, 1994), and the extent of cortical excision along the *Y* (anterior-posterior) axis was measured. The posterior most point of resection within the fusiform gyrus in CAH patients was averaged to be at $y = -13$ (range: 1 to -27) in the left CAH patients and $y = -23$ (range:-4 to -49) in right CAH patients. Thus in the great majority of patients the extent of resection does not extend into the region of peak activity for face processing within the fusiform gyrus that was found in the Kanwisher study (Kanwisher et al., 1997) (L fusiform: average y = -63, range = -41 to -75; R fusiform: average y = -55, range = -39 to -69). Based on the data from Crane's sample, we are confident that the SAH and CAH patients in our study have similar extents of resection of mesial structures and no excision in the specified fusiform face area.

## Materials

The Dade Face Learning Test (DFLT) consisted of 48 faces: 12 original photographs and 36 altered images. From each original face three altered faces were created using digital image software (Knoll, Hamburg, & Pawliger, 1994). Each altered image differed from the original face only by the configuration of the facial features (eg. distance between eyes, height of forehead, size of mouth, etc.; see Figure 1). Six original faces and six altered faces were chosen to create the learning set. The remaining three images for each target face were distributed amongst three recognition-foil sets. Hence, each recognition set consisted of 24 faces: the 12 target faces and 12 foil faces. Three test forms were created, with the recognition tests occurring in different orders. Two pilot studies were carried out on a total of 154 healthy undergraduate students (mean age: 22; range: 18-47) in order to determine

Figure 1

Set of four face stimuli: Target face in upper left corner (in box), with foil faces from the three foil sets.



test difficulty, equivalency of recognition sets, and item effectiveness. The first pilot study provided valuable information about the effectiveness of individual stimuli and the level of difficulty of the test itself. Based on the results of this initial study, six faces underwent further modification, and the order and distribution of foil items were changed across sets to equate for level of difficulty. The second pilot study was carried out using the modified version of the test to verify the effectiveness of the new items, and to further validate that healthy subjects could learn the specific target faces and retain this information over time.

## Procedure

Prior to testing, subjects were shown a demonstration face with two examples of foil stimuli to familiarize them with the task. The actual test entailed four presentations of the 12 target faces, with recognition trials occurring after the first presentation (Single Exposure Recognition trial; SER), after the fourth presentation (Fourth Exposure Recognition trial; FER), and after a 24-hr delay (see Figure 2). For encoding, faces were presented one at a time for four seconds each with a four-second interstimulus interval. For recognition, faces were again presented serially and subjects had to indicate yes or no if the current face was exactly the same as one of the 12 target faces. Scores were obtained by adding correct hits (max=12) and correct rejections (max=12) for a total possible score of 24.

### Discrimination test.

In order to clarify if patients had difficulties in discriminating between target and foil faces, a discrimination test was added. Forty-four of the total number of subjects participated in this task (LR = 12; RR= 10; NC=26). The discrimination test consisted of 12 pairs of faces

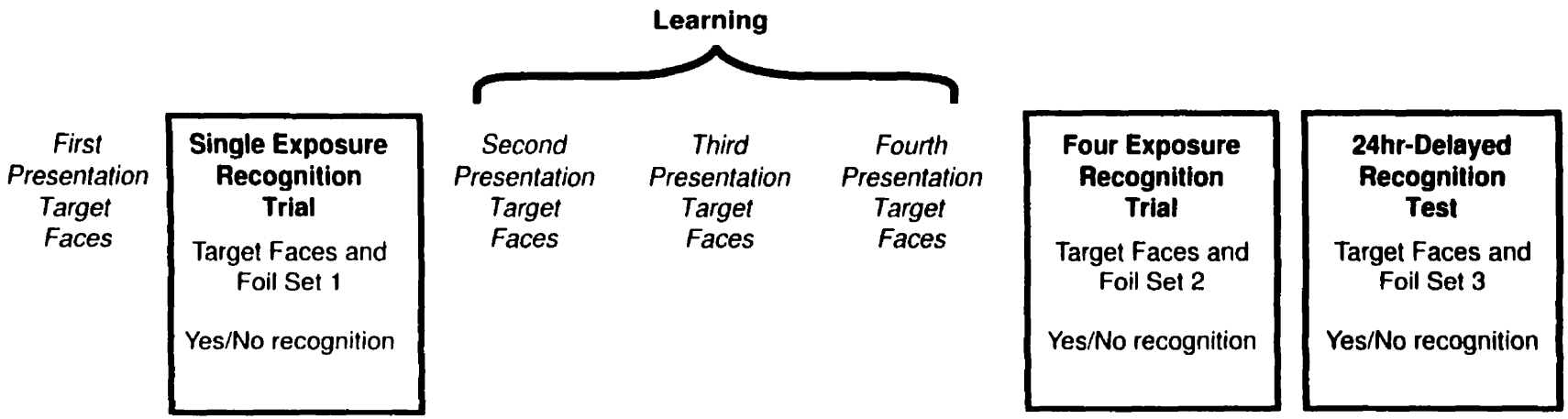



Figure 2
Schematic representation of the experimental paradigm.

from the learning test: six target-target pairs and six target-foil pairs. Subjects had to state for each pair whether the faces were the same or different. Scores consisted of the total number of correct same/different discriminations (max=12; chance=6).

## Results

As the number of SAH patients was small, statistical analyses were carried out to determine if the data from the SAH and CAH patients could be collapsed together into left and right resection groups. Two separate repeated measure ANOVAs were carried out (one for the left-sided patients and one for the right) using Group (CAH vs. SAH) as the between subjects factor. No significant differences were found between left CAH and SAH patients ($F_{1,17} = 2.7$; $p = 0.1$), or between right CAH and SAH patients ($F_{1,15} = 2.1$; $p = 0.2$). Consequently, patients were assigned to one of two groups based on the hemisphere of resection (right resection [RR] and left resection [LR]), regardless of their specific type of surgery (CAH or SAH).

### Face Learning and Recognition Test

A two-way repeated measures ANOVA was performed, comparing the three groups (LR, RR, and NC) on memory performance for the three times of testing (SER, FER, and the 24hr delayed recognition test). The analysis showed a main effect of group ($F_{2,69} = 11.1$, $p<0.001$) and a main effect of time of testing ($F_{2,138} = 41.5$, $p<0.0001$). There was no significant interaction ($F_{4,138} = 2.0$, $p< 0.1$). A post-hoc Tukey test for unequal N's revealed that the right resection group performed significantly worse than the healthy control ($p = 0.007$) and the left resection ($p = 0.007$) groups. There was no significant difference between the left resection and healthy control groups ($p = 0.6$). A

second post-hoc test of the main effect of Time-of-testing revealed that performance on the Fourth Exposure trial was significantly better than on the Single Exposure trial ($p<0.001$), and than on the 24-hr delay test ($p<0.01$). Performance after the 24-hr delay was significantly better than on the Single Exposure trial ($p<0.001$) (see Figure 3).

## Discrimination Test

A one-way ANOVA comparing the three groups on the discrimination task showed that both the patient groups performed as well as the healthy control group ($F_{2,45} = 0.5$, $p< 0.6$). (see Figure 4)

## Classification

To investigate whether the DFLT can aid in the classification of patients according to side of temporal lobe resection, the individual scores for each trial were examined to determine an appropriate cut-off score. Performance on the Single Exposure trial was more variable across subjects, and appeared less predictive than Fourth Exposure trial scores. Therefore, only the scores from the Fourth Exposure trial and the 24hr-delayed recognition test (which both showed greater differences between groups than did the Single Exposure trial; see Figure 3) were used to calculate an optimal cut-off score. The two scores were combined and averaged for each individual. The average of the combined scores was 19.0 (range = 15-21.5) for the LR group, and 16.8 (range = 13-21.5) for the RR group. A cut-off score of 18 on this measure correctly classified 15 of the 19 LR patients, and 14 of the 17 RR patients. Test sensitivity (the true positive rate) was calculated as the number of times the test correctly classified RR patients, divided by the total number of RR patients, multiplied by 100 (Fleiss, 1985). Specificity (the true

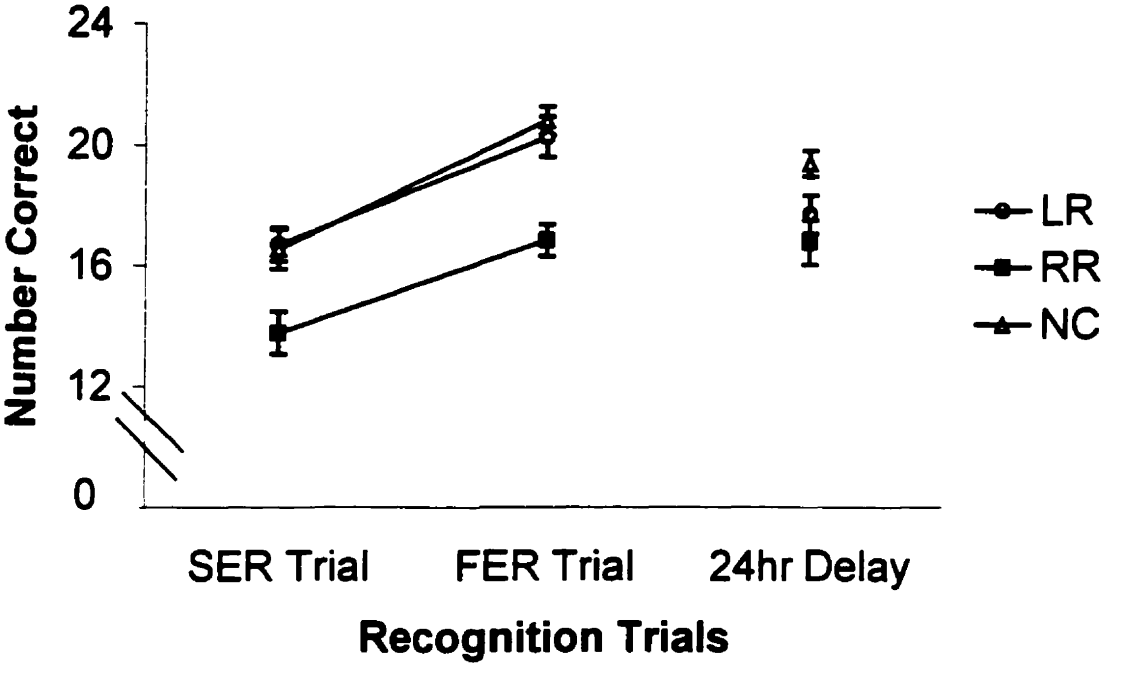



Figure 3

Face recognition memory scores: group X recognition test, showing mean number of faces correctly identified as ones seen previously, or as new faces. Three recognition tests: the single exposure recognition trial (SER) following the first presentation of 12 target faces, the fourth exposure recognition trial (FER) after three additional presentations of the target faces, and a recognition test following a 24hr delay interval. LR = Left resection, n= 19; RR = Right resection, n= 17; NC = Normal control, n=36

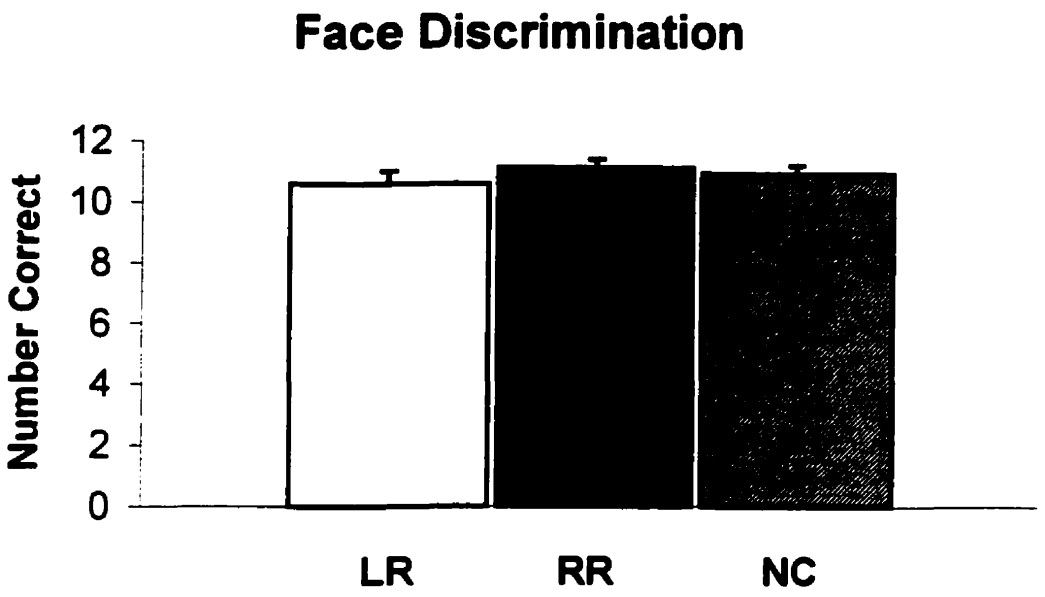



Figure 4

Mean face discrimination scores of LR (left resection: n = 12),

RR (right resection: n = 10) and NC (normal control : n = 26) subjects.

negative rate) was the number of times the test correctly rejected a LR patient, divided by the total number of LR patients, multiplied by 100 (Fleiss, 1985). This resulted in good sensitivity and specificity scores of 82% and 79%, respectively.

## Discussion

The findings of the current experiment are in concordance with earlier studies that have shown face recognition deficits in patients with right hemisphere lesions (Benton & Van Allen, 1968; De Renzi & Spinnler, 1966; Milner, 1968; Morris et al., 1995; Warrington & James, 1967). Clearly, proficiency in face learning and recognition are associated with the integrity of the right temporal lobe. Importantly, data from postoperative patient MRIs at the Montreal Neurological Institute (Crane, 1999) indicate that the extent of resection rarely invades the fusiform face area. Also, results of the face discrimination task in the current study suggest that the function of these face perception regions remains intact: performance of the LR and RR groups is not significantly different from the healthy control subjects (see Figure 4). Thus, patients are not impaired due to an inability to perceive the differences between the face stimuli, but are impaired due to a deficit in face memory processing.

An advantage of the DFLT is that, unlike other face recognition measures, it is possible to examine learning and retention after a long-term delay interval, and this may aid in detecting individual deficits where previous tests did not. As discussed by Jones-Gotman (Jones-Gotman et al., 1997), tests that examine performance over multiple trials are less susceptible to transient, random, fluctuations in an individual's performance that may be unrelated to a primary memory impairment. Using a multiple trial procedure also

revealed the same pattern of learning and retention as shown previously, using a different kind of nonverbal material (abstract designs) in patients with abnormality in the temporal lobe (Jones-Gotman, 1996; Jones-Gotman et al., 1997; Majdan et al., 1996): right resection patients showed poor face learning, but little or no forgetting after a 24hr delay interval, and left resection patients did not differ from normal subjects. This means that the pattern is not specific to one type or nonverbal material, and may reflect a difference between the hemispheres in basic function.

The task used to assess face learning and memory in this experiment is unusual, and most closely resembles the real-world situation of discriminating faces of identical twins. The subtlety of the face configuration changes allows for examination of the learning process for facial features. However, the novelty of the DFLT and its particular format raises the question as to whether face responsive brain regions are the principal areas used to process these particular stimuli. In another research paradigm, electrophysiological studies of epilepsy patients showed that blurred pictures of faces were treated the same as intact face photos, and did not significantly change the amplitude of N200 event related potentials in ventral face-specific processing sites (McCarthy, Puce, Belger, & Allison, 1999). This suggests that blurred, or even somewhat distorted, faces are recognized by face processing areas in the brain. Thus, it is probable that the face stimuli in the current experiment activated face-processing regions, as all the items appeared as intact faces, and subjectively, individuals perceived the stimuli as real faces: they did not appear as caricatures, nor as abnormal configurations of facial features.

Additional evidence that the DFLT engages face-responsive brain regions is obtained from a PET study that used the current face stimuli and a similar 'yes-no' recognition paradigm to examine encoding and recognition (Dade et al., 1997). During an encoding PET scan subjects viewed new faces that they were required to remember. During a long-term recognition scan subjects had to recognize the exact faces that they had learned four days previously. Functional brain imaging data from the long-term recognition condition minus the face-encoding condition revealed increased bilateral fusiform face activity in the region of the FFA and in the right inferior temporal gyrus (this region was also noted during a face-repetition condition in a different face encoding study (Kuskowski & Pardo, 1999). Face encoding minus long-term recognition showed greater activity in the left superior temporal sulcus, a region associated with the perception of movement, facial expression and head and eye orientation (see Haxby et al., 2000, for review). Hence, face processing regions clearly participate in the encoding and recognition conditions of this task.

Examination of data from patient studies and healthy subjects in PET on the same task allows a broader assessment of the participation of brain regions during face processing. Imaging studies of healthy subjects provide information about numerous brain regions that participate in a particular task, while findings from patients with specific brain lesions provides information about what regions are *necessary* for successful completion of that task. For example, functional imaging studies of face recognition have consistently shown bilateral fusiform and bilateral occipitotemporal activity during face processing tasks (Haxby et al., 1994; Kanwisher et al., 1997; McCarthy et al., 1997; Puce et al., 1996; Sergent et al., 1992). However, the performance

of the patients in the current study clearly shows that the structures in the right hemisphere play a more critical role in the learning and later recognition of faces.

Hence, the question arises: which of the structures that are included in the resection are responsible for the face recognition deficit? Surgical treatment of temporal lobe epilepsy usually includes excision of regions of the amygdala, hippocampus and varying extents of the temporal cortex (Trop et al., 1997). However, resection rarely invades the fusiform face area (Crane, 1999). Patients also performed like normal subjects on the face discrimination test (see Figure 4), indicating that their impairment is a deficit related to memory processing rather than perception.

Role of the Hippocampus

Several studies have attempted to elucidate the role of mesial temporal lobe structures in face memory but the findings have been equivocal. Milner (1968) examined the relationship between extent of hippocampal resection and face recognition performance. In one of three experiments, patients with large right hippocampal removals were found to be significantly impaired relative to patients with right temporal neocortical removals with little, if any, hippocampus removed. However, on the other two experiments no significant difference in recognition performance was found between patients in whom the hippocampus had been spared and those in whom it had been radically excised (Milner, 1968). Miller, Lai and Munoz (1998) employed several memory tests including the face memory portion of the WRMT to examine the performance of epilepsy patients in relation to pathology of excised amygdaloid, hippocampal and entorhinal tissues. Postoperative specimens of these temporal lobe structures were examined for cell loss and gliosis, and patients were then classified based

on which mesial structures were considered abnormal. All patients had the same anterior temporal lobe resection. But, postoperatively only those patients who did not have significant hippocampal cell loss or gliosis, as determined by pathology, were impaired on face memory tasks when compared to healthy control subjects. This finding indicates that resection of intact hippocampal tissue impairs face recognition. Unfortunately, in this study patients with left or right resections were grouped together; therefore issues of laterality cannot be addressed.

One study, using the WRMT as a measure, examined pathology of hippocampal tissue in relation to the side of dysfunction (Baxendale, 1997). This researcher reported that unoperated epilepsy patients who had cortical dysgenesis as well as hippocampal sclerosis (as determined by MRI evaluation) performed worse on face recognition than patients with hippocampal sclerosis alone, regardless of the side of their pathology (Baxendale, 1997). However, these results should be interpreted with caution, as the number of subjects with cortical dysgenesis was small (n = 9; 4 right and 5 left) compared to the number of subjects with hippocampal sclerosis (n=90). In a subgroup of patients who underwent an en bloc resection from a temporal lobe, surgical specimens of hippocampal tissue were examined for neuronal density. No correlation was found between patients' preoperative performance on the face portion of the WRMT and right hippocampal CA1 neuronal density (Baxendale, 1997).

Interestingly, in a review of 33 studies including a total of 112 amnesic patients of diverse etiologies, subjects with focal lesions of the hippocampus, fornix or mammillary bodies were found to be unimpaired on WRMT face recognition (Aggleton & Shaw, 1996). The authors suggest that although these patients had severe amnesia, there was

sparing of recognition abilities under some test situations. This finding seems somewhat unusual in the instance of amnesia, but the possibility that subjects could complete this type of face recognition task based on familiarity judgements (which might be spared), rather than on recollection based judgements (which could be impaired), is discussed. They also found that four patients with bilateral amygdala damage performed poorly. It is suggested that this deficit is related to a failure to take advantage of affective cues in the faces. However, the number of subjects with amygdala lesions was small, so the significance of this finding remains unclear.

Role of Anterior Temporal Cortex

The lack of correlation between right hippocampal cell loss and face recognition performance in the Baxendale study (1997), hints at involvement of other temporal lobe regions in face memory. Findings from studies of non-human primates suggest that regions of the temporal cortex are highly involved in visual recognition (Fahy, Riches, & Brown, 1993; Horel, 1993; Meunier, Bachevalier, Mishkin, & Murray, 1993; Miyashita, 1993). A study of visual response properties of neurons in behaving monkeys showed that neurons in the ventral portion of the anterior temporal pole responded more to complex visual stimuli (including faces) than to simple stimuli (Nakamura, Matsumoto, Mikami, & Kubota, 1994). Moreover, activity in these neurons corresponded to the visual recognition performance of the monkeys, further supporting the notion that anterior temporal cortex is involved in visual cognition (Nakamura et al., 1994).

Findings of anterior temporal-lobe participation during face processing have also been noted in studies of human subjects. Brain imaging of famous-face processing has revealed greater bilateral anterior middle temporal activity when comparing viewing of

famous faces to viewing newly learned faces (Leveroni et al., 2000), and greater left anterior temporal lobe activity when comparing viewing of famous faces to viewing famous names (Tempini et al., 1998). Recognition of familiar faces is more complex than simply recognizing structural features, and involves knowledge of personal identity and name generation (Tempini et al., 1998; Valentine, Bredart, Lawson, & Ward, 1991). Thus the results of these two imaging studies suggest a role for the anterior temporal region in long-term memory and semantic processing of face stimuli. However, participation of the anterior temporal lobe region is not limited to recognition of familiar faces. In a PET study of encoding of novel faces, significant correlations were found between cerebral blood flow in anterior temporal lobe regions and face memory performance (Kuskowski & Pardo, 1999). In electrophysiological studies of epilepsy patients, Allison and colleagues (Allison, Puce, Spencer, & McCarthy, 1999) discovered face-specific P350 event-related-potentials in the anterior ventral temporal lobe that, unlike the bilateral activity that occurred in other temporal lobe regions, occurred only in the right hemisphere. Together these findings fit with the model of Bruce (1983) that proposes that the right hemisphere is preferentially involved in the processing and memory of facial features and configuration, while left temporal regions are engaged with semantic processing of names, occupations and other person-specific information.

The importance of the anterior temporal lobe in face processing has also been raised in discussions of prosopagnosia. Damasio and colleagues (Damasio, Tranel, & Damasio, 1990) proposed that the "amnesic associative" type of face agnosia was caused by bilateral damage in anterior temporal lobe regions (including hippocampus and temporal cortex). Allison and colleagues (Allison et al., 1999) suggest that, given their

highly lateralized finding of face-specific processing in the right anterior ventral region of the temporal lobe, damage to this area alone might be sufficient to produce amnesic prosopagnosia. This outcome from unilateral anterior temporal damage seems unlikely, as the RR patients in the current study have had resection within this anterior face area, and none have the symptomatology of prosopagnosia. However, these RR patients do have a significant deficit in face learning as compared to LR patients, supporting the importance of the right anterior temporal region, including the hippocampus, in learning and maintaining the memory of the configuration of facial features.

Although the right temporal region is important to this task, the exact roles of the hippocampus and the anterior temporal cortex remain unclear. Within the right CAH and SAH patients in this study, the common area of resection is from mesial temporal-lobe structures, and specifically from hippocampus, supporting the importance of the hippocampal region on this task. Thus, our current results are in concert with earlier findings that showed that the right hippocampus plays an important role in nonverbal learning (Jones-Gotman, 1986; Jones-Gotman, 1996). The function and level of participation of the anterior temporal cortex on this type of task remains unclear. However, future insights may be gained through the use of functional brain imaging techniques with patients and healthy subjects.

## Clinical Utility

As face processing and memory appear to involve specific regions within the right anterior temporal lobe, and the current test has shown that RR patients as a group are impaired, the question arises as to whether this testing paradigm might be clinically useful for neuropsychological evaluations of individuals. As an initial step in

investigating this possibility, the sensitivity and specificity scores for classification of the current patients were examined. Hermann and colleagues (Hermann et al., 1995) found that the face-discrepancy index scores for the WRMT (Word score minus Face score) rarely misclassified LR patients as having a right resection (specificity = 90%), but the sensitivity to RR patients was low, correctly identifying only 31% of those with a removal from the right temporal lobe. A different study, using the raw scores for the WRMT face test, found that this measure had a sensitivity score of 65% with a specificity score of 75% (Morris et al., 1995). The scores for the DFLT are clearly an improvement over the results with the WRMT face task, correctly predicting 82% of RR patients (sensitivity), and correctly rejecting 79% of LR patients (specificity).

Unfortunately, tests that have shown clear differences in groups of postoperative temporal lobe patients have failed to show the same predictive ability in unoperated epilepsy patients (Delany, 1982; Hermann et al., 1995; Jones-Gotman, 1996). Preoperative localization of the epileptic lesion in epilepsy patients can be difficult, as a unilateral seizure focus can cause seizures that spread and interrupt function in the contralateral hemisphere (Oxbury, 2000). Other pre- to post-operation performance differences can occur for many possible reasons. First, unoperated patients are suffering from seizures that are coming from brain tissue that is only partially dysfunctional. Hence, prior to surgical removal, such tissue may still participate to some extent in its various cognitive roles, decreasing any preoperative deficit. A second possibility is that, due to early damage, some reorganization has taken place and an area close to the seizure focus has taken over that particular cognitive function. However, at the time of surgical excision this region is removed in conjunction with the more severely damaged tissue. A

third possibility is that the surgical removal disconnects functioning brain areas and those regions are not able to perform certain cognitive tasks as efficiently following surgery due to the loss of those connections. Consequently, multiple factors may cause tests to be less accurate in predicting the side and site of dysfunction in unoperated epilepsy patients. Nevertheless, a hemisphere that is impaired should show some signs of dysfunction, and thus more comprehensive testing approaches are required to detect subtle deficits.

Other differences that affect the accuracy of face-memory tests in predicting the hemisphere of dysfunction are related to the lateralization of face-memory processing in the general case, and to precise lateralization in the individual case. In general, face processing has been shown to increase neuronal activity bilaterally in temporal-lobe regions (Tempini et al., 1998; Haxby et al., 2000; Haxby et al., 1994; Kanwisher et al., 1997; Leveroni et al., 2000; McCarthy et al., 1997; Puce et al., 1996; Sergent et al., 1992). Therefore, although the right hemisphere plays a more substantial role than the left in face memory, dysfunction within face processing regions in the left hemisphere may interfere with function in the more proficient right hemisphere, causing secondary impairment. Another possibility is that the loss of the contribution of the left hemisphere in face processing may itself be detrimental. Lateralization in the individual also needs to be considered, as although bilateral fusiform activity is common, activity of the left fusiform is more variable across individuals (Kanwisher et al., 1997). Hence, some individuals may maintain right hemisphere dominance for face processing, but the proportion of the task carried by the left hemisphere may vary, resulting in some individuals showing a lesser degree of right hemisphere dominance. Thus, a patient with

left temporal lobe damage and less lateralization of function (i.e. more left hemisphere participation in face processing) may be impaired on a face memory task. This, however, is a situation of inaccurate prediction of lateralization of dysfunction due to the individual's weak dominance, and not a failure of the test to detect a true impairment in this individual's abilities.

## Conclusion

More investigation is required to understand fully the neuronal system that is involved in face learning and recognition. In concordance with previous studies of nonverbal (design) learning (Jones-Gotman, 1996; Jones-Gotman et al., 1997; Majdan et al., 1996), our findings indicate that the right hippocampus plays an important role also in learning of facial configuration. Nevertheless, future studies are required to understand the role and interactions of other temporal-lobe regions, such as the anterior temporal cortex, in face learning and recognition. Toward this aim, the DFLT provides a more thorough evaluation of face recognition memory than previous face memory tasks. This paradigm has greater sensitivity to resection from the right temporal lobe within individual subjects, thus providing a further step towards improving the tools needed to gain a more comprehensive understanding of the face memory system.

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Connecting text

In the first manuscript of this thesis, the results of the two complementary olfactory memory studies (the patient study and the PET study) supported an equivalent role for left and right temporal lobe structures in odor learning and recognition. In Chapter 3, which investigated nonverbal processing of visual material (faces), the same types of patient groups were tested utilizing the same learning and recognition paradigm as had been used in the olfactory studies. However, the results were quite different. Patients with resection from the right temporal lobe showed a clear deficit in face recognition, while patients with a left resection did not perform differently from control subjects. In Chapter 4, the results of a corresponding face memory PET experiment with healthy subjects will be presented. As was the case with the olfactory studies, the PET face study uses the same face stimuli and similar testing paradigm as in the patient study, which will allow broader interpretations as results from these two complementary methodologies can be compared and considered together.

# Chapter Four

## Experiment Four

## A PET study examining encoding, short-term, and long-term recognition of facial-feature configuration

Lauren A. Dade, Robert J. Zatorre, and Marilyn Jones-Gotman

In the study described in Chapter 3, only the group of patients with resection from the right temporal lobe was impaired on my face learning test, while the performance of the corresponding left resection group was indistinguishable from the healthy control group. This complementary PET experiment was designed to investigate which structures in the temporal lobe are most responsible for face recognition, and to examine the differential involvement of brain regions during face encoding, and short-and long-term recognition.

All three conditions were subtracted directly from each other, resulting in three comparisons: encoding versus short-term recognition, encoding versus long-term recognition, and short-term versus long-term recognition. This approach provides a powerful comparison for assessing differences in memory processing, as subjects are viewing faces in each condition; therefore differences in brain activity between the conditions can be attributed to the differences in cognitive processing demands.

Comparisons between encoding and recognition were examined to determine if there were differences in prefrontal regions, as some researchers claim that the left prefrontal cortex is more involved in episodic encoding, while right prefrontal regions are more involved in retrieval (Hemispheric Encoding and Retrieval Asymmetry, or 'HERA', model) (Buckner, 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). Although the original HERA model did not identify specific regions in the prefrontal cortex, from a later analysis Buckner (1996) identified the left inferior frontal regions [Brodmann areas (BA) 44 and 45] as participating more during encoding (of verbal stimuli), and a right anterior frontal region (Brodmann area 10), as participating more in recognition.

Differences in temporal lobe activity during recognition as compared to encoding were also examined, as was the question of possible hemispheric asymmetry related to the predicted right hemispheric dominance for the task.

Predictions with regard to the detection of fusiform activity were tentative due to the nature of the subtraction analyses. By using a subtraction technique, if a region were equivalently active across all conditions, no significant differences would be detected in the subtractions. The fusiform is clearly important in face perception (Allison et al., 1994; Haxby, Hoffman, & Gobbini, 2000; Kanwisher, McDermott, & Chun, 1997; McCarthy, Puce, Gore, & Allison, 1997; Puce, Allison, Asgari, Gore, & McCarthy, 1996), and this region should therefore be active in all conditions, given that subjects are seeing faces in the three conditions. However, it would be of interest to see if there would be differences based on the memory requirements of the task, showing greater activity in either encoding, short-term or long-term recognition.

The stimuli used for this experiment were a large subset from the Dade Face Learning Test (DFLT). I have shown in Chapter 3 that the DFLT is more sensitive in detecting right temporal lobe dysfunction than the Warrington face memory test according to recent studies (Hermann, Connell, Barr, & Wyler, 1995; Morris, Abrahams, & Polkey, 1995). For the PET experiment, two modifications were made: first the test material was divided into two stimulus sets to allow examination of short-term and long-term recognition, and second, as there is evidence for further memory consolidation over longer time periods (McGaugh, 2000), a four day delay interval was selected for long term recognition.

## Method

### Subjects

Twelve healthy right-handed volunteers (6 men, 6 women) participated in this study (mean age = 24.8; range = 20 - 30 yrs). None had a previous history of neurological or psychiatric disorders. This study was approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital. Subjects gave informed written consent and were paid for their participation.

### Stimuli

The 12 target faces and 24 of the foil faces from the DFLT (Chapter 3) were used in this experiment. The face stimuli from the DFLT were created by altering the configuration of facial features of twelve original photographs using a computer software program (Knoll, Hamburg, & Pawliger, 1994); a detailed description of the stimuli is provided in Chapter 3. The entire stimulus set consisted of 48 faces, which were further divided into 12 sets of four highly similar faces. The twelve target faces consisted of six altered faces and six original ones. The remaining three faces from each set were distributed amongst three different recognition foil sets. In the PET experiment, six of the target faces were used as stimuli for a long-term recognition scan and six were used as target stimuli for a short-term recognition scan. Foils were distributed among the four different recognition conditions, which occurred during either a training session or during the PET scan. Images were presented in the center of a computer monitor. Subjects gave their response via a 'yes-no' key press.

Procedure

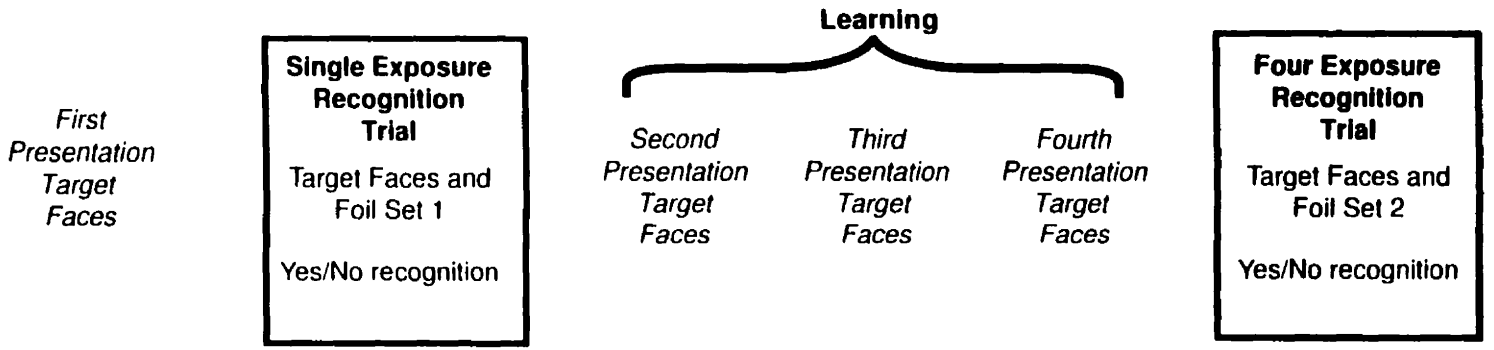
Training Session.

Subjects were trained on the face recognition task four days before the PET study. All faces were presented for four seconds with a six second interstimulus interval. Subjects were shown the six long-term (LT) target faces, followed by the first recognition test (6 targets, 6 foils). The target faces were then shown again for three additional serial presentations, followed by a second recognition test (6 targets, 6 new foils). The final long-term recognition test occurred four days later during the PET session.

PET Session.

Subjects participated in the following scanning conditions four days following the training session: long-term face recognition, encoding of new faces, and short-term face recognition. All conditions included presentations of six faces over the 60-sec scanning interval, with the conditions occurring in the same order for all subjects. Twelve stimuli were presented for each recognition task, with six presentations during the scanning interval. In order to ensure that imaging would reflect potential face recognition, four to five of the target stimuli were shown during the PET data acquisition window. Stimuli were presented at the same rate as during training (4-sec with a 6-sec interstimulus interval) and responses were given via key-press, with a random key-press response given during the encoding task. The short-term target faces (not seen before) were presented during the encoding scan. Three additional presentations occurred without scanning prior to the short-term recognition scan in order to approximate the number of exposures subjects had experienced for the long-term target faces. (Figure 1)

## Training Session




## PET Session four days following Training Session

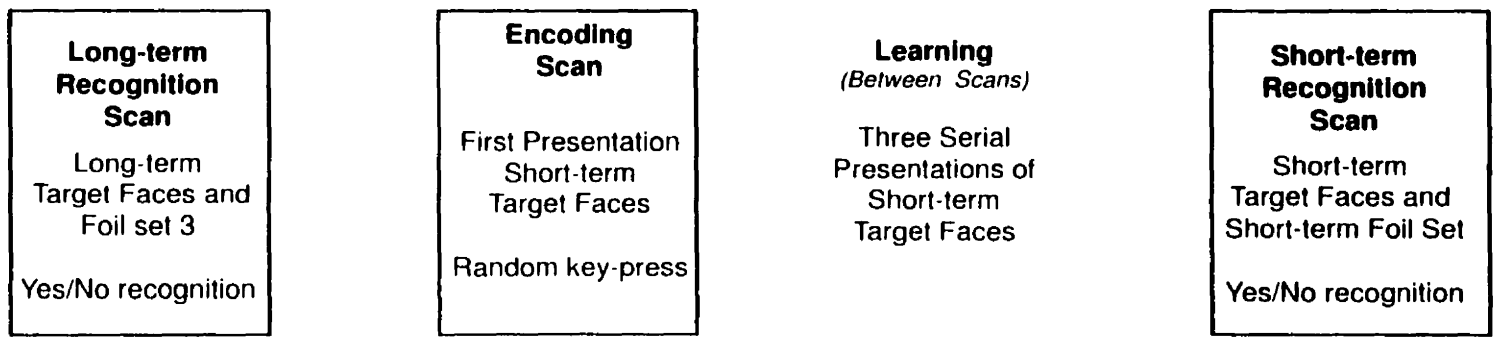



Figure 1
Schematic representations of the experimental paradigm

Data Acquisition and Analysis

PET scans were acquired using a CTI/Siemens EXACT ECAT HR+ scanner with an intrinsic resolution of 4.2mm x 4.2mm x 4.2mm. The distribution of cerebral blood flow (CBF) was measured during a 60 second scanning interval using the $^{15}O$ water bolus method (Raichle, Martin, Herscovitch, Mintum, & Markham, 1983). T1-weighted whole brain magnetic resonance imaging scans (~140-160 1mm sagittal slices) were attained with the use of either a Siemens Vision (1.5T) or a Philips ACS III (1.5T) scanner. CBF images were reconstructed using a 14-mm Hanning filter, and normalized for differences in global CBF. PET and MRI scans were co-registered and linearly transformed into standardized stereotaxic space (Evans et al., 1992; Talairach & Tournoux, 1988). Differences in regional CBF were measured by paired image subtraction between the scans of interest. A *t*-statistic map was created by dividing the CBF difference at each voxel by the mean standard deviation of normalized CBF across all intracerebral voxels (Worsley, Evans, Marrett, & Neelin, 1992). The method for assessing the significance of CBF was assessed by a method based on three-dimensional Gaussian random field theory. The threshold for significant *t*-statistic peaks for a total of 182 resolution elements (14x14x14mm) for a grey matter volume of $500cm^3$ was set at $t \geq \pm 3.53$, yielding a false-positive rate of 0.58 and an uncorrected p-value of <0.0004.

## Results

Behavioral Results

Subjects performed well on all recognition tests. Their mean percent correct during training was 86% on the first recognition and 94% on the recognition trial

following four exposures to the target stimuli. Mean percent correct during PET was 88% for long-term delayed recognition and 76% on the short-term recognition. A one-way repeated measures analysis of variance for recognition tests one, two, and four-day delayed recognition (all for the same target faces) showed no significant difference in performance across the three trials ($F_{2,22}$= 2.0, p = 0.15). A paired *t*-test comparing performance between the short- and long-term recognition PET tasks revealed significantly better performance on the long-term recognition task ($t_{11}$=2.6, p≤ 0.02; two-tailed).

PET Results

Encoding minus short-term recognition.

An examination of the regions showing greater activity during encoding than during recognition (as compared independently to the short-term and then the long-term conditions), was expected to reveal areas that play a more substantial role in face encoding than in either of the recognition memory stages. Although greater activity was expected in left prefrontal regions during encoding, only one region in the left frontal polar cortex (BA 10) was found, and medial activity within the cingulate gyrus that spread into left and right frontal cortex. The remaining frontal activations occurred in supplementary motor cortex (BA 6). The region showing the greatest number of significant areas of activity in this subtraction was in the left precuneus (BA 7). All other significant regions of activity can be noted in Table 1A.

Table Legend for Tables 1, 2, and 3

Numbers in parentheses refer to Brodmann areas. Brain regions are indicated by Talairach and Tournoux (Talairach & Tournoux, 1988) stereotaxic coordinates (in mm) X, Y, and Z: *X* is the medial to lateral distance relative to midline (positive = right hemisphere), *Y* is the anterior to posterior distance relative to the anterior commissure (positive = anterior), *Z* is the superior to inferior distance relative to the intercommissural plane (positive = superior).

Table 1

**1A**. Areas showing greater activity during encoding than short-term recognition

| Location | X | Y | Z | *t* statistic |
|---|---|---|---|---|
| *Frontal Lobe* | | | | |
| L frontal polar cortex (10) | - 5 | 68 | 12 | 3.7 |
| Bilateral cingulate gyrus (32) | 0 | 37 | -12 | 4.7 |
| L middle frontal gyrus (6) | -30 | 20 | 54 | 4.1 |
| L superior frontal gyrus (6) | -21 | 8 | 53 | 4.5 |
| *Parietal Lobe* | | | | |
| L precuneus (7) | - 3 | -44 | 44 | 6.7 |
| Bilateral cingulate gyrus (31) | 1 | -50 | 29 | 4.1 |
| L precuneus/cingulate (7/31) | -15 | -54 | 30 | 4.1 |
| L precuneus (7) | -16 | -68 | 24 | 4.6 |
| L superior parietal lobule (7) | -16 | -52 | 63 | 4.1 |
| L angular gyrus (39) | -50 | -54 | 27 | 5.0 |
| R angular gyrus (39) | 46 | -61 | 26 | 5.4 |
| *Occipital Lobe* | | | | |
| L area 19 | -12 | -78 | 39 | 4.2 |

**1B**. Areas showing greater activity during encoding than long-term recognition

| Location | X | Y | Z | *t* statistic |
|---|---|---|---|---|
| *Frontal Lobe* | | | | |
| Bilateral cingulate gyrus (32) | 1 | 37 | -15 | 3.6 |
| L superior frontal gyrus (6/8) | -23 | 8 | 51 | 4.8 |
| R superior frontal gyrus (6/8) | 20 | 6 | 62 | 3.5 |
| L medial frontal lobe (6) | - 7 | - 4 | 59 | 3.6 |
| R precentral gyrus (4) | 9 | -32 | 59 | 4.2 |
| *Temporal Lobe* | | | | |
| L superior temporal sulcus (21/22) | -62 | -47 | 3 | 4.5 |
| L superior temporal gyrus (39) | -55 | -62 | 21 | 3.5 |
| *Parietal Lobe* | | | | |
| L inferior parietal lobe (40) | -55 | -40 | 47 | 3.5 |
| L precuneus (7) | -24 | -42 | 48 | 3 5 |
| Bilateral precuneus/cingulate (7/31) | 1 | -44 | 38 | 5.3 |
| L cingulate gyrus (23) | -13 | -49 | 28 | 3.6 |
| Bilateral precuneus (7) | 1 | -50 | 51 | 5.5 |
| L precuneus | -21 | -57 | 18 | 4.1 |
| Bilateral precuneus (7) | 0 | -61 | 30 | 4.8 |
| R precuneus (7) | 11 | -64 | 39 | 3.5 |
| L superior parietal lobe (7) | -21 | -64 | 53 | 3.5 |
| R angular gyrus (39) | 44 | -64 | 27 | 4.5 |

Encoding minus long-term recognition.

This subtraction revealed brain regions that showed greater levels of activity during encoding as compared to the long-term recognition condition. In this comparison, as in the comparison of encoding to short-term recognition, areas of activity were noted in prefrontal regions, with the majority being in supplementary motor areas (BA 6/8). More striking were the numerous areas of activity within the parietal lobe, and specifically in the region of the precuneus (BA 7), bilaterally. In this comparison greater activity was noted during encoding than in long-term recognition within the left temporal lobe: in the superior temporal sulcus (21/22) and the superior temporal gyrus (39). Coordinates (Talairach & Tournoux, 1988) for all regions of significant activity can be found in Table 1B.

Short-term recognition minus encoding

In keeping with the HERA hypothesis, this subtraction revealed significantly greater activity within right prefrontal regions, specifically, in right frontal polar cortex (BA 10) and right mid-dorsolateral prefrontal cortex (BA 9, 9/46). Bilateral activity was noted in the ventrolateral regions (right BA 10/47 and left BA 47). Significant differences were also noted in left and right visual cortices (BA 17 and 18). All areas showing significant differences in activity are recorded in Table 2A (see Figure 2 for illustration).

Long-term recognition minus encoding.

Subtraction of encoding from long-term recognition revealed a majority of activations in the right hemisphere, as anticipated. Areas of increased activity were noted

Table 2

**2A.** Areas of greater activity during short-term recognition than encoding

| Location | X | Y | Z | *t* statistic |
|---|---|---|---|---|
| *Frontal Lobe* | | | | |
| R frontal polar cortex (10) | 27 | 53 | - 3 | 5.1 |
| R mid-dorsolateral frontal (9) | 27 | 49 | 15 | 4.1 |
| R mid-ventrolateral frontal (10/47) | 40 | 43 | - 5 | 5.2 |
| R mid-doroslateral frontal (9/46) | 42 | 30 | 21 | 4.6 |
| Bilateral cingulate gyrus (32) | 0 | 24 | 26 | 3.5 |
| R orbitofrontal cortex (11) | 17 | 22 | -18 | 3.6 |
| L mid-ventrolateral frontal (47) | -32 | 20 | - 9 | 3.5 |
| R inferior frontal gyrus (44) | 47 | 15 | 27 | 3.6 |
| *Insula* | | | | |
| R insula | 32 | 25 | 0 | 5.4 |
| L insula | -40 | 17 | 0 | 3.8 |
| *Parietal Lobe* | | | | |
| R inferior parietal (40/7) | 47 | - 44 | 48 | 3.5 |
| *Occipital Lobe* | | | | |
| R area 17 | 4 | - 78 | 6 | 4.6 |
| R area 18 | 24 | - 93 | - 5 | 6.0 |
| L lingual gyrus (17/18) | -11 | - 97 | - 9 | 4.1 |
| L lingual gyrus (17/18) | - 9 | -100 | 14 | 4.0 |

**2B**. Areas of greater activity during long-term recognition than encoding

| Location | X | Y | Z | *t* statistic |
|---|---|---|---|---|
| *Frontal Lobe* | | | | |
| R orbitofrontal cortex (11) | 20 | 20 | -15 | 4.7 |
| *Parietal Lobe* | | | | |
| L postcentral gyrus (1) | -42 | - 25 | 44 | 3.7 |
| *Temporal Lobe* | | | | |
| R inferior temporal gyrus (37) | 54 | - 57 | -14 | 5.2 |
| *Occipital Lobe* | | | | |
| R fusiform gyrus (37) | 31 | - 45 | -15 | 3.6 |
| L fusiform gyrus (37) | -35 | - 52 | -17 | 4.3 |
| R fusiform gyrus (18) | 23 | - 92 | - 6 | 4.8 |
| R fusiform gyrus (19) | 35 | - 64 | - 6 | 3.7 |
| R inferior occipital gyrus (19) | 47 | - 77 | - 9 | 4.1 |
| R middle occipital gyrus (18) | 38 | - 85 | 29 | 3.5 |
| L area 17 | - 4 | - 99 | - 5 | 4.5 |
| R area 17/18 | 18 | -100 | 9 | 4.9 |
| *Cerebellum* | 5 | - 57 | -18 | 3.6 |

Figure 2.

Areas of significant activity during face recognition conditions as compared to face encoding shown using averaged PET *t*-statistic maps of CBF increases for 12 subjects, superimposed on their averaged MRI image. The color scale to the left indicates the range of the *t*-values. The short-term recognition (ST) minus encoding subtraction is on the left and reveals the significant regions of activation in right prefrontal and occipital cortex; the long-term recognition (LT) minus encoding is on the right and reveals the activity in lateral inferior right temporal cortex. See Table 2 for precise locations of all significant activations.

ST-Encoding

LT- Encoding

Z = -5

Z = -12

in the right orbitofrontal cortex and right inferior temporal gyrus and right occipital gyri. Significantly greater activity was noted in area 17 in left and right visual cortex. Although there was bilateral fusiform activity, there were a greater number of significant activations in the right fusiform gyrus. See Table 2B for a complete description of all significant activations and their locations within Talairach space (Talairach & Tournoux, 1988) (see Figure 2 for illustration).

Short-term recognition minus long-term recognition.

Comparison of these two recognition conditions to each other revealed greater participation of the right hemisphere, within right frontal lobe regions (BA 10 and 9), right inferior parietal lobe and precuneus. One area of greater activation was detected in left frontal polar cortex (BA 10). Refer to Table 3. (see Figure 3 for illustration)

Long-term recognition minus short-term recognition.

Interestingly, only three areas showed greater activity during long-term than short-term recognition, this was in bilateral fusiform gyrus (BA 37) and right inferior temporal gyrus (BA 37).(see Table 3, see Figure 3 for illustration)

## Discussion

An examination of the regions showing greater activity during encoding than during recognition (as compared independently to the short-term and then the long-term conditions) was expected to reveal areas that play a more substantial role in face encoding than in either of these two other memory stages. The most notable finding was the significantly greater activity in the parietal lobe during encoding than in either of the recognition conditions. Numerous significant peaks were noted bilaterally in the region of the precuneus (BA 7), with this activity being more prominent in comparison to long-

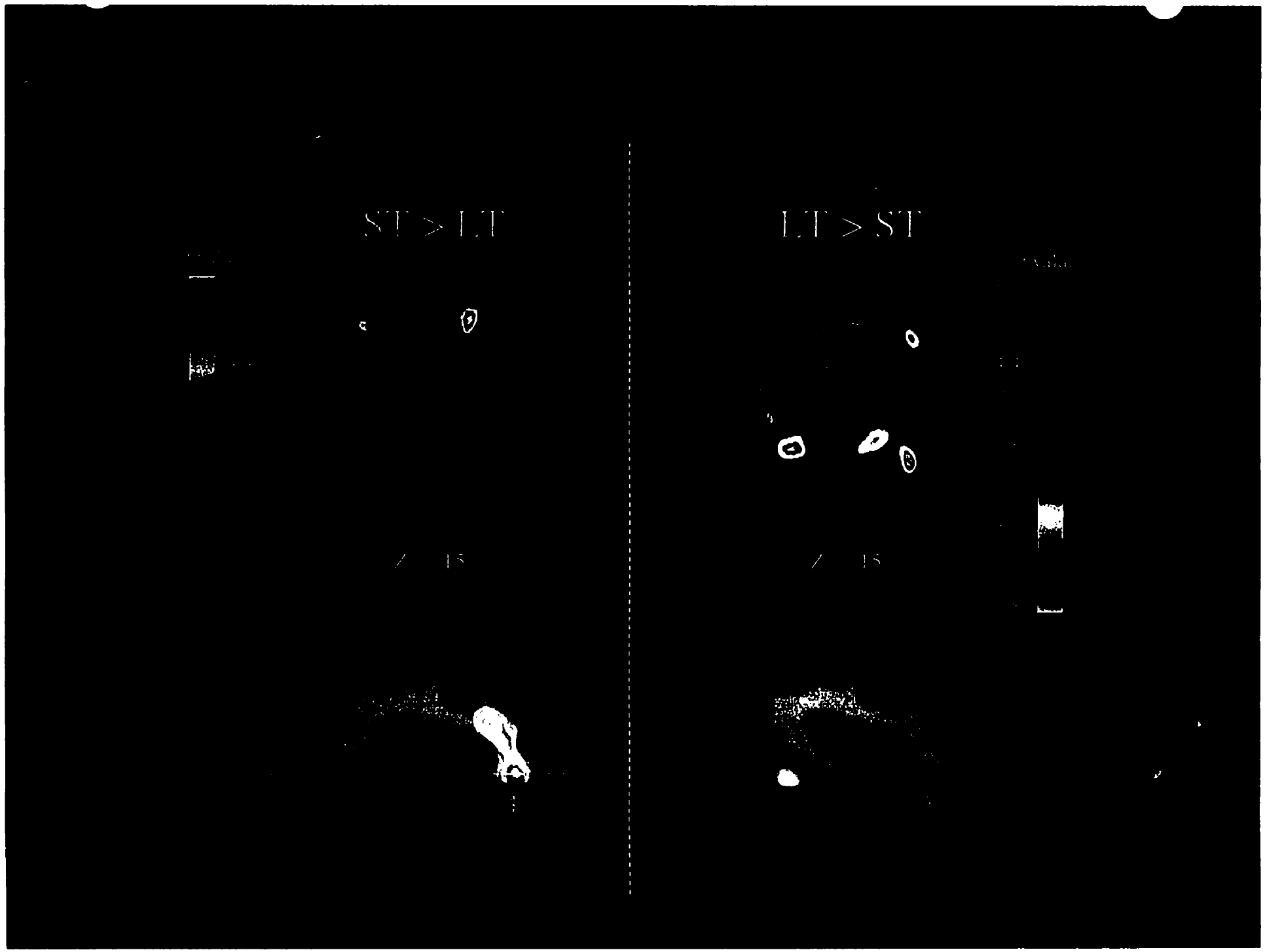
Table 3. Changes in CBF observed for short-term minus long-term recognition

| Areas showing greater activity during the short-term condition | | | | |
|---|---|---|---|---|
| Location | X | Y | Z | *t* statistic |
| L frontal polar cortex (10) | -38 | 61 | - 5 | 3.9 |
| R frontal polar cortex (10) | 28 | 49 | 5 | 3.8 |
| R frontal polar cortex (10) | 38 | 43 | -12 | 4.4 |
| R mid-dorsolateral frontal (9) | 38 | 25 | 18 | 4.0 |
| R inferior parietal lobe (40) | 46 | -42 | 50 | 3.6 |
| R Precuneus (7) | 12 | -57 | 44 | 5.6 |
| Bilateral calcarine sulcus (17) | 1 | -76 | 8 | 3.9 |

| Areas showing greater activity during the long-term condition | | | | |
|---|---|---|---|---|
| Location | X | Y | Z | *t* statistic |
| L fusiform gyrus (37) | -32 | -52 | -15 | 4.1 |
| R fusiform gyrus (37) | 30 | -47 | -15 | 3.6 |
| R inferior temporal gyrus (37) | 54 | -61 | -18 | 4.6 |

Figure 3.

Areas of significant activity during short-term recognition versus long-term recognition shown using averaged PET *t*-statistic maps of CBF increases for 12 subjects, superimposed on their averaged MRI image. The color scales indicate the range of the *t*-values. Regions of greater levels of activity during short-term recognition as compared to long-term recognition are shown on the left and reveal the significant regions of activation in right prefrontal cortex. Regions of greater activity in the long-term recognition (LT) minus the short-term recognition condition are on the right and reveal the significant areas of activity in bilateral fusiform and right inferior temporal cortex. See Table 3 for precise locations of all significant activations.


ST > LT
LT > ST

term recognition as opposed to short-term recognition. Recent studies have shown participation of the precuneus in mental imagery, during mental navigation (Ghaem et al., 1997) and motor imagery (Ogiso, Kobayashi, & Sugishita, 2000). A recent fMRI study has also associated activity in this region in relation to visual attentional shifts (Nagahama et al., 1999). Hence the increased activity occurring during encoding compared to recognition may reflect subjects attempting to make a mental image of the stimuli and the shifts in their attention to the different facial features. Interestingly, both of the recognition conditions elicited greater bilateral occipital activity, which may reflect more scanning of the actual face stimuli than occurred during encoding. In regard to the function of parietal cortex in memory processing, some researchers suggest that its function extends beyond imagery. A recent study by Krause and colleagues (Krause et al., 1999) showed consistent increases in parietal activation during episodic memory retrieval for both highly imaginable and abstract words, supporting a specific memory function unrelated to imagery, and other authors have also reported significant increases in parietal activity during retrieval (Schacter et al., 1995; Tulving et al., 1994). The current finding of strong parietal activity during encoding as compared to recognition is interesting, because it suggests that there is a stronger participation in some parietal regions during the initial memory stages. This has not been discussed previously, as long-term versus encoding comparisons have rarely been made.

In consideration of the HERA model (Tulving et al., 1994), differential activity between encoding and recognition in the prefrontal regions was of interest. Surprisingly, there were relatively few significant peaks in prefrontal regions during encoding in comparison to either of the two recognition conditions. The majority of frontal regions

showing greater activity were in the supplementary motor cortex (BA 6/8) – not a region known to be important for visual memory. Conversely, significant regions of right prefrontal activity during short-term recognition were apparent in comparison to both the encoding condition and the long-term recognition condition. Dorsolateral and ventrolateral prefrontal regions are known to be important in working memory (Goldman-Rakic, 1995; Owen, 1997; Petrides, 1995; Ungerleider, Courtney, & Haxby, 1998). Hence, this finding suggests that material is being held 'online' in working memory regions during the 5 to 8 minute delay interval between the last learning presentation (between scans, see Figure 1) and the short-term recognition scan.

Activation within temporal lobe regions was of particular interest, in relation to my patient findings (Chapter 3). No significantly greater areas of activity were noted in the temporal lobe regions during encoding as compared to the short-term recognition condition. However, in the comparison between encoding and long-term recognition, significantly greater activity was noted in the left superior temporal sulcus (BA 21/22) and the left superior temporal gyrus (BA 39) during encoding. The superior temporal sulcus has been noted as a face-responsive region in other imaging studies, and appears to be involved in the perception of changeable aspects of the face, such as eye orientation (see Haxby, 2000, for review). However, as these findings occurred in the left temporal region, they do not aid in explaining the deficit of the right resection patients in my patient study. This finding does, however, raise an interesting speculation that this could account for the left temporal deficits that are seen on single-trial face memory tasks, where the efficiency of encoding will impact particularly strongly on recognition.

In the comparison between short-term and long-term recognition, subjects' lower behavioural performance during short-term recognition was unexpected. It was anticipated that subjects would perform at the same level on the two tasks, or perhaps slightly better on the short-term recognition condition, as in this condition they had most recently seen the target items. The short- and long-term recognition tasks were the same, in that the stimuli were of the same type, all faces were of the same quality, not degraded or blurred. Also, the number of learning trials and the number of items to recognize on the two tasks was the same, as was the rate of presentation. The difference in performance between these two conditions may be due to a combined effect of less efficient learning of the stimuli when they are presented to subjects within the scanner, and perhaps due to the benefits of memory consolidation over a four-day delay interval, as reflected by the better long-term recognition performance.

The comparison of activity during short-term as compared to long-term recognition continued to reveal greater prefrontal activity during short-term recognition, as was noted in the short-term versus encoding comparison. These findings are consistent with other short-delay recognition (Grady et al., 1995) and working memory (Dade, Jones-Gotman, Zatorre, & Evans, 1997; Haxby, Ungerleider, Horwitz, Rapoport, & Grady, 1995) imaging studies examining face recognition. Short-term recognition elicited more mid-dorsolateral and frontal regions, particularly within the right hemisphere, than in the long-term recognition condition. Two factors that have been shown to influence activity within prefrontal cortices (Barch et al., 1997; Braver et al., 1997) are memory load and the rate of presentation of items, and these were not different for the two recognition conditions. In addition, there was no degradation of the stimuli

[another factor that may influence activity in prefrontal regions (Haxby et al. 1995)] on either of the tasks, all the performance requirements for the two recognition conditions were the same. Therefore, the findings suggest that the differences in the level of prefrontal activity were related to the differential delay interval between encoding and the earlier versus later recognition tests.

In the long-term recognition as compared to encoding and short-term recognition, there was significantly greater activity noted in the right inferior temporal gyrus, and in the fusiform gyri within left and right ventral occipitotemporal regions. Two regions of fusiform activity in the long-term minus encoding subtraction (-35x, -52y, -17z; 31x, -45y, -15z), and the two areas of significantly greater fusiform activity in the long-term minus short term subtraction (-32x, -52y, 15z; 30x, -47y, -15z) were very close to the coordinates of Kanwisher et al (1997) for the Fusiform Face Area, -35x, -63y, -10z and 40x, -55y, -10z. The findings of greater participation of left and right fusiform during long-term recognition suggest an equivalent role for these structures in face processing. However, from the findings of the patient study in Chapter 3, a strong role for the left temporal lobe in face recognition is not supported.

It is not clear how findings of fusiform participation in face recognition apply to the patient results, as measurements of patients' resections (Crane, 1999) indicate that the Fusiform Face Area is rarely invaded. Interestingly, across the two recognition conditions (in comparison to encoding), there are a greater number of significant regions of activity within the right hemisphere, specifically within the right frontal lobe and the posterior right occipitotemporal regions. Also in a PET study by Kuskowski & Pardo (1999) significant correlations were found between cerebral blood flow in anterior temporal lobe regions and face memory performance. These findings suggest that impaired face recognition in

patients with resection from the right temporal lobe results from dysfunction in right temporal regions other than the Fusiform Face Area.

Clearly the fusiform region is important for face perception, and likely it continues to function despite surgical resections from the anterior temporal lobe. This was demonstrated by the similar performance of the patient and healthy control groups on the face discrimination task as described in Chapter 3. Face memory is a higher level of cognitive processing than is face perception, and it must call upon additional right anterior temporal regions that may not have been revealed here if this region participated to the same extent on all memory conditions. For instance, if similar increases in blood flow occurred in a brain region during encoding and recognition, then when these two conditions were subtracted from one another no significant differences in activity would be apparent. Further PET studies that use comparisons to lower level baseline tasks are required to address this question adequately.

Overall this experiment has allowed a comparative evaluation of regions involved in three memory processing stages, revealing differences in the participation of prefrontal cortices during encoding, short-term and long-term recognition, as well as highlighting the greater participation of fusiform regions during long-term memory processing. The strong participation of right prefrontal regions during short-term recognition and the greater involvement of the right inferior temporal gyrus during long-term versus short-term recognition supports a larger role of the right hemisphere for face memory. Furthermore, findings of left temporal involvement during face memory processing (as in the encoding minus long-term subtraction) may help to explain the poor performance of left temporal lobe epilepsy patients on single exposure recognition tests, and therefore

also clarify why these tests have difficulty in correctly classifying patients to side of seizure focus (Hermann et al., 1995; Morris et al., 1995).

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## Connecting text

The previous studies have examined and compared learning and long-term retention for two types of nonverbal stimuli: odors and faces. In this final manuscript, a third type of memory processing – working memory – is investigated. The aim of this study was twofold: first to study olfactory working memory, a phenomenon that has not been a focus of research previously, and second to determine if olfactory working memory engages the same prefrontal cortical regions as working memory for other types of nonverbal stimuli. In order to address these objectives, healthy subjects underwent functional imaging (PET) while carrying out two working memory tasks: olfactory and visual (face).

## Chapter Five

# Working memory in another dimension:

# Functional imaging of human olfactory working memory.

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Submitted to *Neuroimage*

Abstract

The majority of working memory research has been carried out within the visual and auditory modalities, leaving it unclear how other modalities would map onto currently proposed working memory models. In this study we examined the previously uninvestigated area of olfactory working memory. Using positron emission tomography we measured cerebral blood-flow changes in twelve volunteers during an olfactory working memory task and a comparison visual working memory task. Our findings indicate that, on a broad anatomical level, olfactory working memory engages similar prefrontal regions as those involved in processing visual working memory. In order to advance our conceptual viewpoint in the area of working memory, research needs to continue to expand beyond the traditional areas of vision and audition.

Working memory involves the short-term maintenance and active manipulation of information required to complete complex cognitive tasks. Animal and human studies have shown that lateral prefrontal cortex subserves working memory function (for review, see Owen, 1997, and Ungerleider, Courtney & Haxby, 1998). However, although the importance of this region in working memory is apparent, its functional organization is not fully understood. Current experiments usually focus closely on the functional subdivisions described in the working memory model of Baddeley (1986). This framework consists of a central executive processor, which acts as an attentional controller, and two slave systems that are responsible for holding and manipulating information: the *phonological loop*, which registers and stores verbal information, and the *visuospatial sketchpad*, which consists of both an object processor and a spatial processor.

Although this model has proven to be successful, Baddeley himself has described it as incomplete (Baddeley, 1996). While it describes how auditory and visual modalities can access the phonological and visuospatial processors, it is unclear how the other senses of touch, taste, and smell would map onto such a system. Clearly, we carry out working memory processes when using these other senses. For example, when shopping one may assess the firmness of several different tomatoes, maintaining this tactile information 'on-line' before making a selection. Food and drink, such as fruit, coffee, and wine, are often selected by 'on-line' comparisons and monitoring of olfactory cues, not to mention the ongoing monitoring and mental comparisons of aromas and flavors that take place while cooking. Despite these day-to-day experiences, the presence of a short-term memory system in olfaction has been debated; however there is evidence to advocate a distinction between short and long-term memory in olfaction (see White,

1998, for discussion). Therefore, if these other sensory systems have short-term memory components, do they map onto the phonological, visual, or spatial processing systems, or are there additional sensory slave systems that contribute information to the central executive processor - and do these other modalities utilise the *same* executive processor? Although there have been investigations as to how the frontal lobes are organized in terms of their function, and in relation to the described informational domains, the effects of the *modality* of the input have rarely been discussed, and issues about senses other than vision and audition have not been addressed.

Within the realm of working memory, the basis of organization of the prefrontal cortex is highly debated. Differing models tend to divide function of the prefrontal cortex along similar anatomical divisions: dorsolateral and ventrolateral frontal cortex. However, the basis for the division of function between the two regions is quite different. For example, Goldman-Rakic (1995) has suggested that the functional compartmentalization of the prefrontal cortex is based strictly upon the informational domain of the stimulus input, proposing multiple segregated processing areas each devoted to one type of knowledge domain. This 'domain-specific' working memory hypothesis suggests that the inferior convexity of the frontal lobe (Brodmann area [BA] 47/12) is specialized for the processing of the nonspatial aspects of objects and faces (O'Scalaidhe, Wilson & Goldman-Rakic, 1997; Wilson, Scalaidhe & Goldman-Rakic, 1993), that left ventral cortex (BA 44) is involved in verbal working memory, while the dorsolateral frontal cortex (BA 9/46) subserves processing of spatial working memory (Courtney, Ungerleider, Keil & Haxby, 1996; Levy and Goldman-Rakic, 1999). Within this model, different sensory modalities can contribute to one informational domain (for

example, both auditory and visual stimuli can contribute to the "spatial domain"), and it is possible that each "module" supports its own domain-specific executive functions (Levy and Goldman-Rakic, 1999).

However, there is evidence contrary to the theory of a spatial versus nonspatial division between the dorsolateral and ventrolateral cortices. For example in single-cell recording studies of nonhuman primates, the findings of Fuster et al. (Fuster, Bauer & Jervey, 1982) and White and Wise (1999) did not find support for the spatial vs. nonspatial division; these studies indicated that there was no significant segregation of cells responding to spatial and nonspatial cues, and that cells responding to these dimensions were distributed throughout frontal regions. In addition, the findings of Rainer et al. (Rainer, Asaad & Miller, 1998) showed that some prefrontal neurons can simultaneously convey both "what" and "where" information, making the idea of simple segregation of these functions a more complex issue.

An alternative model of the functional division of prefrontal cortex, which does not depend on this spatial vs. nonspatial partition, has been proposed by Petrides (1994,1995). According to the "two-level hypothesis," division of the lateral frontal cortex is based upon the executive functions that the mid-dorsolateral and the mid-ventrolateral regions carry out rather than upon the stimulus modality that is being processed. The mid-ventrolateral frontal cortex (BA 45 and 47/12) is involved in the active encoding and retrieval of information that is held in posterior cortical association areas, while the mid-dorsolateral frontal cortex (BA 9 and 46) is involved with ongoing monitoring and manipulation of information. Therefore, it is the nature of the cognitive process rather than the information domain that dictates the activity of these areas.

Nonetheless, the possibility of additional differentiation of function occurring *within* the mid-dorsolateral and mid-ventrolateral frontal regions based on the type of input modality is not ruled out.

Surprisingly, the majority of studies that have compared working memory models have used only the visual modality (see Owen, 1997, for review) and have not investigated some of the other sensory modalities, such as smell. Therefore, in the present study we aimed to: 1) investigate working memory in a previously uninvestigated sensory modality (olfaction) using a low level baseline task to reveal the entire pattern of working memory activity; 2) compare and contrast functional brain activity during olfactory working memory to working memory processes within a more studied modality (vision); and 3) determine if these two disparate modalities would activate either distinctly different or highly similar regions of prefrontal dorsolateral and/or ventrolateral working memory areas.

Olfactory processing was chosen, as it is known to have several major differences from the other sensory modalities. Anatomically, the olfactory system is unique: it has direct contact between the external environment (olfactory receptor cell) and the brain (first synapse, the olfactory bulb), sensory information is relayed to the cerebral cortex *without* an initial relay to the thalamus (Powell, Cowan, & Raisman, 1965), and cortical olfactory areas are phylogenetically older than other sensory cortical areas (allocortex vs. isocortex). Cognitively, memory retention for odors can be extremely long (1 year) and odor memory is relatively impervious to retroactive interference (see Herz and Eich, 1995, for review). Face working memory was chosen as a good nonverbal comparison task, as prefrontal activations occurring during both the face and odor tasks can be

compared to findings from previous face working memory results (Courtney, Petit, Maisog, Ungerleider, & Haxby, 1998; Courtney, Ungerleider, Keil, & Haxby, 1997; Haxby, Ungerleider, Horwitz, Rapoport, & Grady, 1995; O'Scalaidhe et al., 1997; Ungerleider et al., 1998) and the reliability of prefrontal activations can be assessed.

We used positron emission tomography (PET) to measure regional cerebral blood flow changes (rCBF) while subjects carried out the *same* working memory task for odors and faces. The odor stimuli are shown in Table 1. We employed a well-known working memory paradigm (Figure 1) that required subjects to indicate whether the item they were currently experiencing was the same or different from an item they had experienced two trials previously (Cohen et al.,1994; Gevins & Cutillo, 1993; Smith, Jonides, & Koeppe, 1996). The same processing demands of short-term maintenance of information as well as ongoing manipulation of information were required for each stimulus type, and the two stimulus modalities derive from different informational domains; therefore it is possible to make clear predictions of prefrontal activity based on the two described models. Consequently, if each of the two tasks activates separate, distinct areas of the prefrontal cortex, this would be consistent with the idea of segregation of function based on stimulus characteristics, in accord with the 'domain-specific' hypothesis of frontal lobe function. Conversely, if the active lateral prefrontal regions (dorsolateral areas: 46, 9, 9/46 and/or ventrolateral areas: 45, 47/12) overlap, this would suggest that the division of function is not based solely upon stimulus type, or modality, but may rely more on task parameters.

Table 1

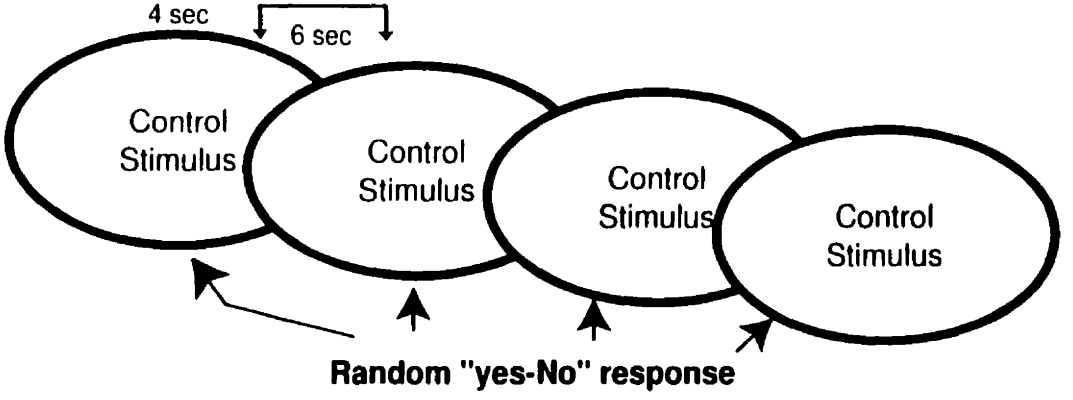
| Odor Category | Odor Stimului |
|---|---|
| Fruity | Peach |
| Floral | Geraniol |
| Minty | Eucalyptus oil |
| Unpleasant | Costus oil |
| Woody | Patchouli oil |
| Spicy | Cinnamon-bark oil |

Odors were presented in puffs of air from opaque squeeze bottles. Odorants were supplied by the Givaudan-Roure Corporation.

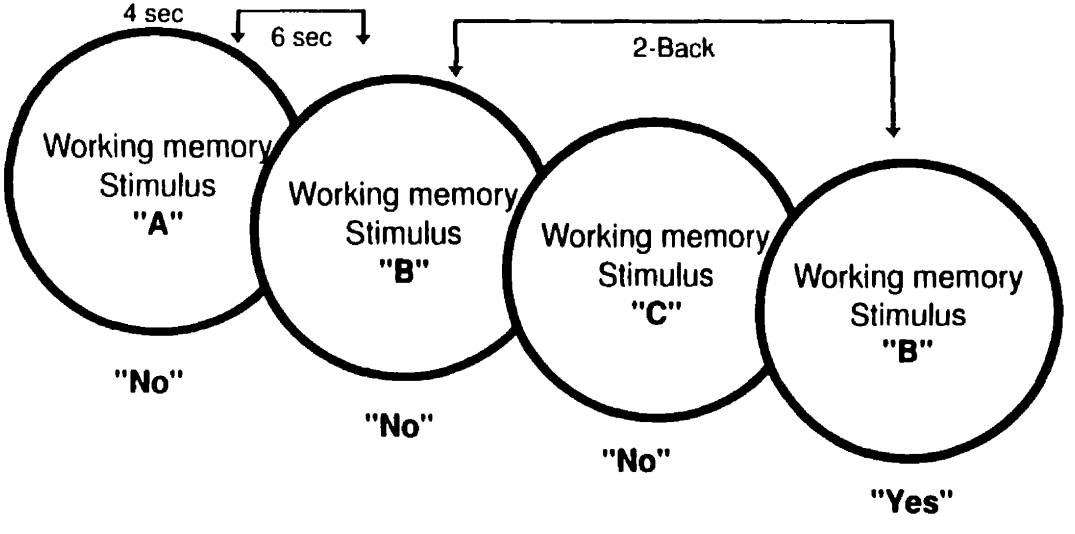
Figure 1.

Schematic diagram of the task procedure. Both the olfactory and visual stimuli were presented using the same paradigm. The two baseline sensorimotor control tasks involved a four second presentation of the control stimulus (olfactory condition: no-odor air puffs; visual condition: scrambled images) with a six second inter-stimulus interval. Subjects gave a random key-press response. During the 2-back working memory tasks, timing of stimulus presentation remained the same (four second stimulus presentation; six second inter-stimulus interval); however subjects had to respond "yes" or "no" via a key-press as to whether the item they were currently experiencing was the same as the one they had experienced 2 trials previously (olfactory condition: odor puffs; visual condition: faces).

**Sensorimotor Control Tasks:**




**Working Memory 2-Back Tasks:**



## Results

### Behavioural Results

Although the stimuli in the two tasks are dissimilar there was no difference in the number of stimuli to be kept active in memory or the length of delay intervals during presentations, factors which have been shown to affect task performance (Barch et al., 1997; Braver et al., 1997). Subjects performed well on both tasks (Odor WM: Mean percent correct 88%, Range 67%-100%; Face WM: Mean percent correct 90%, Range 75-100%). A one-way repeated measures analysis of variance on the two tasks showed no significant difference in the percentage correct ($F_{1, 11}=3.3$ $P>.05$) indicating that these two tasks were adequately equated for level of difficulty. Therefore, differences in rCBF can be more readily attributed to differences in the stimulus modality rather than to differences in task difficulty.

### PET Results

#### Odor working memory minus olfactory baseline.

This subtraction was designed to show areas of activation related to odor processing and activity of prefrontal regions related to working memory function. A directed search in primary and secondary olfactory cortical regions revealed no activation in primary (piriform) cortex, but activity was noted in the left and right orbitofrontal regions. Within the predicted prefrontal cortical areas there were several areas of significant activation: bilateral frontal polar cortex (BA 10), bilateral mid-dorsolateral frontal cortex (BA 9/46), and left ventrolateral frontal cortex (BA 47) (Table 2 and Fig. 2).

Table 2

Numbers in parentheses refer to Brodmann areas. Superscript letters and numbers refer to foci shown in Figure 2. Brain regions are indicated by Talairach and Tournoux (1988) stereotaxic coordinates (in mm) X, Y, and Z: *X* is the medial to lateral distance relative to midline (positive = right hemisphere), *Y* is the anterior to posterior distance relative to the anterior commissure (positive = anterior), *Z* is the superior to inferior distance relative to the intercommissural plane (positive = superior).

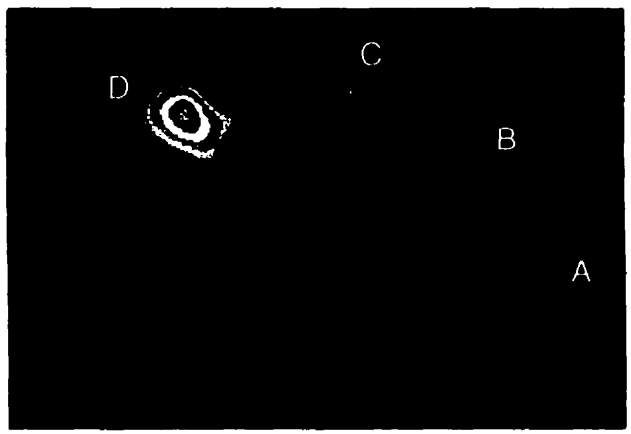
Table 2. Locations of rCBF changes in working memory tasks minus baseline sensorimotor tasks

| | Odor Working Memory | | | | Face Working Memory | | | |
|---|---|---|---|---|---|---|---|---|
| **Location** | **X** | **Y** | **Z** | ***t* statistic** | **X** | **Y** | **Z** | ***t* statistic** |
| **Prefrontal cortex** | | | | | | | | |
| L frontal polar (10/46)[1] | -30 | 53 | 6 | 6.2 | -35 | 51 | 3 | 5.5 |
| R frontal polar (10/46)[A] | 28 | 57 | 0 | 3.4 | 34 | 56 | -2 | 5.6 |
| L orbitofrontal (11) | -27 | 30 | -17 | 3.4 | - | - | - | - |
| R orbitofrontal (11) | 32 | 44 | -18 | 3.0 | - | - | - | - |
| L mid-dorsolateral frontal (46) | - | - | - | - | -28 | 49 | 16 | 5.4 |
| L mid-dorsolateral frontal (46) | - | - | - | - | -39 | 5 | 45 | 4.5 |
| L mid-dorsolateral frontal (9/46)[2] | -40 | 12 | 33 | 4.9 | -42 | 20 | 36 | 3.5 |
| R mid-dorsolateral frontal (9/46)[B] | 39 | 36 | 32 | 4.0 | 38 | 34 | 41 | 4.5 |
| L ventrolateral frontal (47/12)[†] | -51 | 34 | -9 | 3.9 | -46 | 41 | -11 | 3.1 |
| L ventrolateral frontal (45) | - | - | - | - | -32 | 27 | 5 | 4.5 |
| R posterior mid-frontal (32/8) | - | - | - | - | 8 | 20 | 50 | 4.9 |
| **Cingulate Region** | | | | | | | | |
| Retrosplenial cortex | - | - | - | - | 1 | -28 | 24 | 3.7 |
| L paracingulate (32) | -12 | 32 | 30 | 3.7 | - | - | - | - |
| R paracingulate (32) | - | - | - | - | 11 | 30 | 32 | 4.4 |
| R cingulate (32) | - | - | - | - | 16 | 39 | 18 | 4.3 |
| **Motor/Sensory** | | | | | | | | |
| L superior frontal gyrus (6) | -15 | 6 | 53 | 4.3 | -8 | 6 | 62 | 6.4 |
| Superior frontal gyrus (8/6) | 0 | 17 | 57 | 6.3 | - | - | - | - |
| R superior frontal gyrus (6) | 21 | 12 | 56 | 5.2 | 17 | 12 | 56 | 4.3 |
| R superior frontal gyrus (6)[C] | 27 | -4 | 59 | 4.5 | 31 | 3 | 60 | 5.5 |
| L precentral gyrus (4/6)[3] | -30 | -23 | 59 | 5.0 | -32 | -25 | 60 | 5.1 |
| L precentral gyrus (4) | - | - | - | - | -5 | -26 | 59 | 3.6 |
| L dorsal putamen | -28 | 18 | 6 | 3.8 | - | - | - | - |
| **Temporal lobe** | | | | | | | | |
| L middle temporal gyrus (21) | - | - | - | - | -62 | -33 | -8 | 4.0 |
| R middle temporal gyrus (21) | - | - | - | - | 66 | -35 | -11 | 4.4 |
| **Parietal Lobe** | | | | | | | | |
| L superior parietal cortex (7) | - | - | - | - | -13 | -35 | 66 | 3.6 |
| L inferior parietal cortex (40/7)[4] | -44 | -54 | 50 | 5.5 | -40 | -47 | 44 | 7.7 |
| L inferior parietal cortex (40/7) | -28 | -57 | 47 | 6.7 | - | - | - | - |
| L inferior parietal cortex (7) | - | - | - | - | -5 | -64 | 48 | 5.0 |
| R inferior parietal cortex (40/7)[D] | 43 | -54 | 48 | 7.4 | 40 | -56 | 50 | 6.6 |
| R medial parietal cortex (7) | 8 | -69 | 51 | 4.1 | 7 | -68 | 47 | 4.7 |

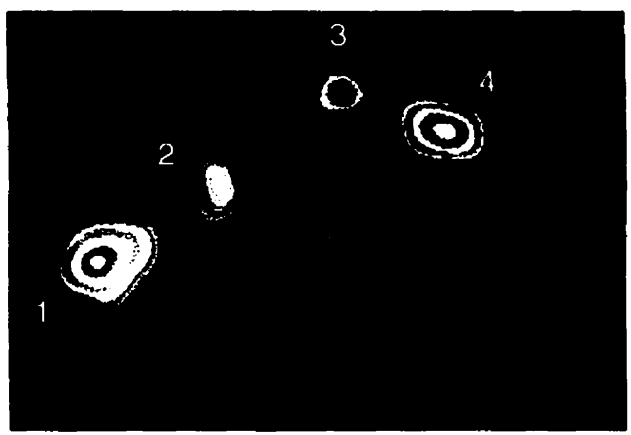
[†] Refer to Petrides and Pandya (1994)

Figure 2. Common areas of activity during olfactory and visual working memory tasks using averaged PET *t*-statistic maps of CBF increases for 12 subjects, superimposed on their averaged MRI image. The color scale to the right indicates the range of the *t*-values. Odor working memory minus the olfactory baseline is on the left, face working memory minus the visual baseline is on the right. Locations of sagittal slices were chosen to illustrate a majority of the relevant activations. Letters designate right hemisphere activations (top of page) and numbers left hemisphere activations (bottom of page). Precise stereotaxic locations of these foci are given in Table 2 and are indicated by the corresponding superscript letter or number. A = frontal polar (BA 10/46); B = mid-dorsolateral frontal (BA 9/46); C = superior frontal (BA 6); D = inferior parietal lobe (BA 40/7). 1 = frontal polar (BA 10); 2 = mid-dorsolateral frontal (BA 9/46); 3 = precentral gyrus (BA 4/6); 4 = inferior parietal lobe (BA 40/7).

Odor Working Memory
minus
Olfactory Baseline

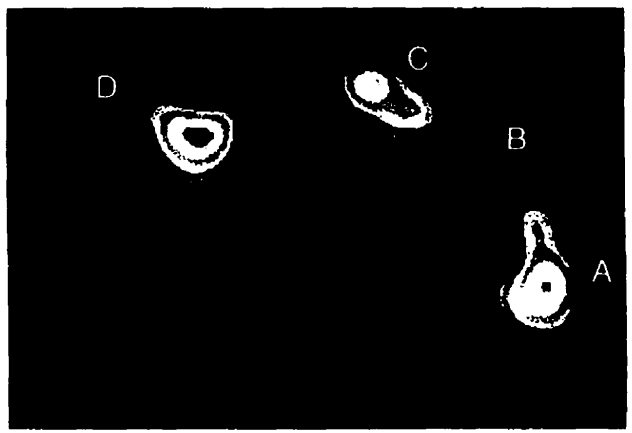



X = 32

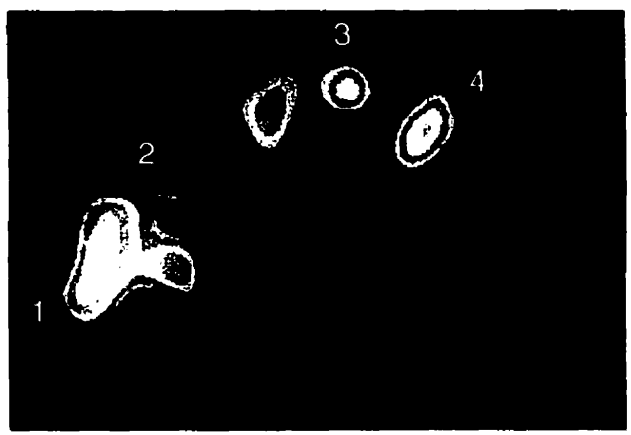



X = -32

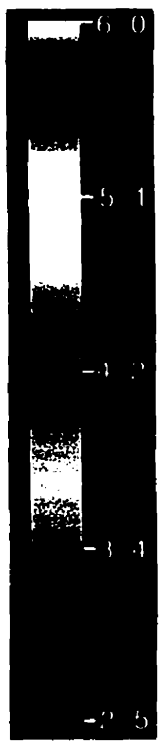
Face Working Memory
minus
Visual Baseline




X = 32




X = -32



Significant rCBF changes outside predicted regions were found in the paracingulate (BA 32), bilateral superior frontal gyrus (BA 6 & 8), left precentral gyrus (BA 4 & 6) and left dorsal putamen (Table 2). No significant areas of activity were noted in the temporal lobes, but several peaks were found in the parietal lobes: right medial parietal cortex (BA 7), and bilateral inferior parietal cortex (BA 40/7).

Face working memory minus visual baseline.

Analysis of the face working memory task minus the visual baseline task was predicted to reveal areas important for face processing and working memory. More specifically, activations were predicted in the fusiform gyrus for face processing (Kanwisher, McDermott & Chun, 1997; McCarthy, Puce, Gore & Allison, 1997) and prefrontal cortical areas (BA 9, 10, 45 and 46) for working memory function (Haxby et al., 1995). No significant activations were noted in the occipital cortex, or in the anticipated fusiform areas. However activity was noted bilaterally in the middle temporal gyri (BA 21) within the occipitotemporal visual processing stream. As with the odor working memory task, significant activations were noted in lateral prefrontal cortex: bilateral frontal polar region (BA 10), bilateral mid-dorsolateral frontal regions (BA 9/46), left mid-dorsolateral (BA 46), and left ventrolateral frontal (BA 45) cortex (Table 2 and Fig. 2).

Significant activations that occurred outside of these predicted areas of interest were found in the cingulate region, bilateral superior frontal gyrus (BA 6), and left precentral gyrus (BA 4). As in the olfactory condition, several rCBF changes were noted in parietal cortex: bilateral inferior parietal cortex (BA 40/7), left superior parietal cortex (BA 7), and right medial parietal cortex (BA7) (Table 2).

Direct Task Comparison.

The olfactory and face tasks have very different sensory processing demands. Therefore, to control for differences at the sensory processing level, we employed a compound comparison between the previous two subtractions using the raw CBF values, subtracting the face-working-memory-minus-visual-baseline scan from the olfactory-working-memory-minus-olfactory-baseline scan. This direct comparison allowed for a more specific examination of the brain activity related to the working memory demands for each condition. Results from this compound subtraction revealed no regions which were significantly more active in the olfactory condition than in the face condition. No prefrontal regions showed significantly more activity during the face task than the olfactory task. Outside this region of interest, two regions showed significantly more activity during the face working memory task. This more sensitive analysis, resulting from the larger number of scans and the comparison of the face to a non-face task, revealed the anticipated activity within the right fusiform gyrus ($t = 4.6$; BA 37; $x = 26$, $y = -44$, $z = -9$). The second region of activity was within the left superior parietal lobe ($t = 3.8$; BA 7; $x = -24$, $y = -76$, $z = 42$).

Conjunction Analysis.

In order to confirm the findings of the compound subtraction we carried out a conjunction analysis with the two contrasts of interest: [odor working memory – olfactory baseline] $\cap$ [Face working memory - visual baseline]. This analysis detects regions where there is a significant main effect of two contrasts, with the interactions among the simple effects excluded (Price & Friston, 1997). Essentially, this conjunction analysis reveals the maximum peaks of activity that are equal in the two contrasts. Using

a conservative *t-value* of 3.5 (Worsley & Friston, in press) to determine areas with significant common activity, four locations were detected in prefrontal cortex: three in dorsolateral region 9/46 (left and right), and one in left frontal polar cortex (10/46). Common activity closely approaching the level of significance was also present in right frontal polar cortex (*t-value* = 3.4). These results further support the findings in the previous subtraction analyses. The Talairach coordinates (Talairach & Tournoux, 1988) for the locations of significant activity in the odor working memory task minus olfactory baseline subtraction, and the face working memory task minus visual baseline subtraction are shown beside the corresponding location of significant common activity detected by the conjunction analysis (see Table 3). All common areas of activity with a *t-value* above 2.9 are included in Table 3.

Table 3. Locations of common regions of increased activity detected in the conjunction analysis, and corresponding regions that were detected in the two separate working memory subtractions.

| | | Conjunction Analysis | | | | Odor Working Memory - Olfactory baseline | | | | Face Working Memory- Visual baseline | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Location** | | **X** | **Y** | **Z** | ***t* statistic** | **X** | **Y** | **Z** | ***t* statistic** | **X** | **Y** | **Z** | ***t* statistic** |
| **Prefrontal cortex** | | | | | | | | | | | | | |
| L frontal polar (10/46) | *A* | **-34** | **51** | **5** | **5.4** | *-30* | *53* | *6* | *6.2* | *-35* | *51* | *3* | *5.5* |
| R frontal polar (10/46) | *B* | **28** | **56** | **- 2** | **3.4** | *28* | *57* | *0* | *3.4* | *34* | *56* | *- 2* | *5.6* |
| L mid-dorsolateral frontal (9/46) | *C* | **-42** | **10** | **41** | **4.2** | *-40* | *12* | *33* | *4.9* | *-42* | *20* | *36* | *3.5* |
| L mid-dorsolateral frontal (9/46) | *D* | **-41** | **20** | **35** | **3.5** | *-40* | *12* | *33* | *4.9* | *-42* | *20* | *36* | *3.5* |
| R mid-dorsolateral frontal (9/46) | *E* | **40** | **36** | **32** | **3.9** | *39* | *36* | *32* | *4.0* | *38* | *34* | *41* | *4.5* |
| L ventrolateral frontal (47/12) | *F* | **-47** | **39** | **-11** | **2.9** | *-51* | *34* | *- 9* | *3.9* | *-46* | *41* | *-11* | *3.1* |
| **Parietal Lobe** | | | | | | | | | | | | | |
| L inferior parietal cortex (40/7) | *G* | **-35** | **-52** | **48** | **5.7** | *-44* | *-54* | *50* | *5.5* | *-40* | *-47* | *44* | *7.7* |
| L inferior parietal cortex (40/7) | *H* | **-44** | **-54** | **50** | **5.5** | *-44* | *-54* | *50* | *5.5* | *-40* | *-47* | *44* | *7.7* |
| R inferior parietal cortex (40/7) | *I* | **40** | **-56** | **50** | **6.6** | *43* | *-54* | *48* | *7.4* | *40* | *-56* | *50* | *6.6* |
| R medial parietal cortex (7) | *J* | **8** | **-69** | **51** | **4.0** | *8* | *-69* | *51* | *4.1* | *7* | *-68* | *47* | *4.7* |

Conjunction peaks *C* and *D* both correspond to a single left mid-dorsolateral prefrontal region of activity detected in the olfactory minus baseline subtraction and a single left mid-dorsolateral prefrontal region detected in the face minus baseline subtraction.

Conjunction Peaks *G* and *H* also correspond to a single point of activity detected in left inferior parietal cortex in the olfactory minus baseline subtraction and the face minus baseline subtraction.

## Discussion

The principal aim of this study was to examine working memory within a previously uninvestigated modality (olfaction), and secondarily, to determine if prefrontal cortical regions, similar to those which have been identified in more heavily researched sensory systems, such as visual memory, are involved in working memory for the olfactory modality. Subjects carried out the olfactory working memory task with no significant difference in behavioral performance from the visual working memory task. Despite the anatomical differences that distinguish the olfactory system from the other sensory modalities (see Introduction), our study showed that prefrontal regions identified during a visual working memory task were also engaged during olfactory working memory.

When comparing the simple analyses of the olfactory and visual working memory tasks minus their appropriate sensorimotor baselines, remarkable similarities in areas of frontal lobe activity were noted. Both working memory tasks displayed increases in activity bilaterally within frontal polar cortex, mid-dorsolateral and ventrolateral frontal lobe areas. In fact, for all prefrontal peaks occurring during the olfactory working memory condition, there was at least one activation occurring in the face working memory condition that was located less than one centimetre distant from that location. Although similar prefrontal regions were activated during the two tasks, a greater number of prefrontal peaks were noted in the face-minus-baseline subtraction, (Table 2). But, these differences were not maintained when the working memory tasks were compared more directly. In the subtraction of the face-minus-visual-baseline-condition from the odor-minus-olfactory-baseline condition no differences in frontal lobe activity were

noted, indicating that for working memory the underlying frontal lobe activations for these two modalities are essentially the same. This finding was further supported by the conjunction analysis, which showed common areas of activation in left and right dorsolateral (9/46)and frontal polar (10/46) cortices (Table 3).

Aside from prefrontal cortical activity related to the working memory condition, other findings were of interest with regard to the specific sensory-processing areas, one of which was the lack of a predicted increase in activity within primary olfactory cortex. The inconsistent occurrence of significant activation in the piriform cortex on olfactory tasks (as compared to baseline tasks) has now been noted in several studies (Dade, Jones-Gotman, Zatorre, & Evans, 1998; Sobel et al., 1998; Zald & Pardo, 1997; Zatorre & Jones-Gotman, 2000), and is of current discussion within the literature (see Zald and Pardo, 2000 and Zatorre and Jones-Gotman, 2000). Sobel et al. (1998) have shown that active sniffing, in the absence of an odor, can activate piriform cortex, raising the possibility of piriform activity occurring during our baseline condition masking any increases due to odor perception. However, whereas there was no significant increase in piriform activation during this working memory condition, the same subjects did show an increase in piriform activity in another condition (not described here, see Dade et al., 1998), when they were smelling the same number of odors and when compared to the *same* baseline condition as in this experiment. This suggests that other factors, aside from sniffing, determine the active participation of piriform cortex in a task. Despite the lack of differential piriform activity, processing specific to olfaction is demonstrated by bilateral activity within orbitofrontal cortex, an area thought to be important in the coding of features of olfactory stimuli (Zatorre &

Jones-Gotman, 2000). Interestingly, it is the activity within the right orbitofrontal cortex, rather than piriform cortex, that appears most consistently across olfactory studies. Activity was also present bilaterally within the insular cortex, which has been shown in animal studies to receive axonal projections from primary and secondary olfactory regions (Price, 1990; Price et al., 1991). Similar insular and peri-insular activity has been noted during other olfactory PET (Sobel et al., 1999; Zald & Pardo, 1997; Zatorre, Jones-Gotman, Evans, & Meyer, 1992), functional MRI (fMRI) (Fulbright et al. 1998), and magnetic source imaging (Kettenmann, Hummel, Stefan, & Kobal, 1997) studies. The insula is thought to be important for gustation (Shipley & Ennis, 1996; Small, Jones-Gotman, Zatorre, Petrides, & Evans, 1997), and it is unclear what proportion of its activity is purely olfactory and what proportion is related to the olfactory system's overlapping relationship with gustatory function.

Also of note with regard to specific sensory-processing regions was the inconsistent detection of fusiform gyrus during the face working memory task. This was not entirely surprising based on the findings of Haxby et al. (1995), which showed a negative correlation between rCBF in fusiform gyrus and increasing working memory delay intervals, with greatest activity shown with one second interstimulus intervals. It is also likely that other differences, such as our shorter overall scanning interval and smaller number of face stimuli, were also contributing factors. However, it is important to note that our delay interval was chosen to follow the time requirements for the olfactory task, and to optimise activity within prefrontal regions, which tend to show greater activity during longer delay intervals (1 sec vs. 8 sec) (Barch et al., 1997). Nonetheless, although neither the presentation interval nor the number of stimuli presented were ideal for

detecting fusiform activation, significant activity was noted in right fusiform gyrus within the direct compound task comparison, which had greater statistical power than the face minus baseline analysis.

Given these results, how do the present olfactory and visual memory findings relate to the different working memory models? In terms of the domain-specific working memory hypothesis it is necessary to substantiate that these two modalities derive from disparate informational domains. Within the working memory model, face stimuli reside in the visual knowledge domain to be interpreted by the "object" processor. It would be difficult to construe odors as belonging to this same domain, as they are neither visual, nor objects in and of themselves. Odors often occur in association with objects or environments: however, when presented without visual cues, even if an odor is familiar, it is difficult to make an odor-object connection (Herz & Eich, 1995). Another question is whether subjects converted both stimulus types into the verbal informational domain through labelling. This is a question that can be applied to many human experiments (including visual 'object vs. spatial' experiments). Can subjects effectively apply verbal labels to stimuli to aid in their recall – changing otherwise nonverbal tasks into verbal ones – and does this alteration result in similarities of brain activity? Although it can be argued that subjects attempted a verbal strategy for remembering the order of items, odors, even familiar ones, are difficult to name when given without contextual cues (Cain, 1979; Richardson & Zucco, 1989; Royet et al., 1999) and people are generally unable to describe a face effectively using language (Meadows, 1974; Milner, 1968). In addition, subjects in the present study had previously experienced a large number of similar scents, decreasing the effectiveness of using a verbal labelling strategy (see

Methods). Therefore, the main source of information about the material presented rests in their sensory specific processing and appropriate nonverbal memory stores rather than transformation into verbal information. Consequently, it is difficult to explain the similarities in activation as due to a conversion of these sensory inputs into a verbal code.

Nevertheless, even if subjects translated one or both of these stimulus types into a verbal code, to then be treated as verbal stimuli, the domain-specific model would predict left ventrolateral activity, *not* dorsolateral activity, as verbal stimuli are not spatial stimuli. Thus, regardless of whether the stimuli were treated as olfactory, visual, or verbal, none of these modalities would be considered spatial, so within the domain-specific model, *none* should preferentially engage the dorsolateral prefrontal cortex (area 9/46). However, in the current experiment the majority of common areas of increased activity in frontal regions occurred within the dorsolateral prefrontal cortex (see Tables 3 and 4).

On the other hand, the two-level processing model predicts that the mid-dorsolateral cortex will be involved regardless of whether the stimuli are visual (Petrides, Alivisatos, Evans, & Meyer, 1993a), olfactory, verbal (Petrides, Alivisatos, Meyer, & Evans, 1993b), or auditory, provided that monitoring of information in working memory is required. Monitoring is clearly involved in the 2-back task, as subjects must continuously monitor the relations between the last three presented items in order to carry out the task. Therefore, our results are consistent with the two-level hypothesis, which suggests prefrontal regions are better divided along lines of function: if two different stimulus types require the same cognitive working memory manipulations, the same prefrontal region would participate. Even if there were differences in location within the

dorsolateral region, this would be consistent with the level of processing model. This model allows for the idea of smaller modality-specific areas occurring *within* each lateral prefrontal region, and this possibility cannot be completely ruled out. Regions 9, 9/46 and 46 are known to maintain preferential connections with multimodal superior temporal sulcus (Petrides & Pandya, 1999), indicating that these regions can receive inputs from a number of sensory sources. However, although it is known that individual neurons may have modality-specific (or domain-specific) responses, it is not clear if these neurons are organized into modality-specific areas in prefrontal regions (Fuster et al., 1982; Rainer et al., 1998; White & Wise, 1999). Although PET is able to show differences in activity between dorsolateral and ventrolateral regions of the prefrontal cortex, its resolution is not currently sufficient to determine if there are small differences in location of increased activity within dorsolateral cortex related to the modality of the task. In future studies, it may be possible to see whether smaller regions of modality specific differences exist within lateral prefrontal cortex using fMRI, which has a greater spatial resolution and the capacity to examine individual differences.

## Conclusion

The multicomponent memory model, with one executive processor and two slave systems, has provided a strong framework for working memory research. However the model itself, and the research that has followed it, has been limited in its sensory view of memory and of human function. For example, it is not clear whether it is the phonological loop, visuospatial sketchpad, or perhaps a separate "olfactory palette" that stores and maintains olfactory information 'on line' for manipulation. Currently our

understanding of working memory is incomplete, and it has not been clear what brain areas are employed in working memory for the "nontraditional" senses of touch, taste and olfaction. To date, working memory models do not clearly address differences that might occur within these other sensory modalities. Therefore, in order to advance our conception of working memory processes the theoretical view needs to be expanded to include these other sensory dimensions.

## Materials and Methods

### Subjects

Twelve right-handed volunteers, six men and six women (mean age = 24.8; range = 20-30yrs) participated in this study. None had a previous history of psychiatric or neurological disorders, no history of nasal injury, and all were non-smokers. Subjects were paid for their participation and gave informed written consent. This study was approved by the Research Ethics Committee of the Montreal Neurological Institute and Hospital.

*Materials.* All visual stimuli were presented in the center of a NEC Multisync display monitor. Six *10 X 12 cm* black and white photographic images of faces were used (3 men, 3 women) for the working memory task. Baseline stimuli were six abstract images that were created by using photo design software. First, the original face images were divided into random sections that were then scrambled; then, edges and face areas that could still be distinguished were blurred resulting in the abstract image. The luminance values for these images were within one standard deviation of the mean measure of luminance for the original face stimuli.

The Givaudan-Roure Corporation provided the odorants. Six odors were used in this experiment (Table 1); however, these subjects participated in five additional olfactory conditions, not described here, and were exposed to a total of 36 odorants from 12 odor categories during their participation in the entire protocol. Overall, subjects were exposed to several odors arising from the same category in order to decrease the effectiveness of verbal labels. Therefore, for example, the use of "minty" as a label would be ineffective as subjects would experience another "minty" odor at a later interval. Discriminability of all odorants was tested, using a three-choice oddball paradigm, on separate groups of 20 healthy control subjects comparing odors within the same category and between an ecologically close category (e.g. minty odors to grassy odors). Mean percent correct discrimination between similar and highly similar scents was 87% (range = 79 – 95%) for the six odors in this experiment. Olfactory stimuli were presented birhinally via opaque squeeze bottles. Baseline scan stimuli consisted of puffs of air from the same type of bottle, without an odorant present.

Procedure

Subjects participated in twelve PET scans of which four were relevant to this study: two sensorimotor control tasks and two working memory tasks. The visual tasks consisted of abstract images presented for the control task and photographs of faces during the working memory task. The olfactory tasks consisted of odorless puffs of air presented for the control task and scented puffs of air during the working memory task. Subjects were told prior to the olfactory baseline scan that no odors would be presented. Order of the conditions (olfactory or visual) was counterbalanced across subjects. Within conditions, baseline scans occurred first and working memory scans second. Each task

consisted of twelve stimulus presentations with six occurring during the 60 seconds of PET data acquisition. Stimuli were presented for four seconds, with a six-second inter-stimulus interval (Figure 1). During the sensorimotor control tasks subjects were asked to make a random key-press following stimulus presentation. Subjects were familiarized with the experimental stimuli prior to the working memory scans. For the working memory tasks, subjects indicated by key-press whether the stimulus they were experiencing was the same or different from the one they had experienced two trials previously ('two-back' task). Prior to the olfactory scans subjects were told to sniff at the same rate and depth of inhalation for all olfactory tasks, whether or not an odor was present.

Scan acquisition and analysis

PET scans were obtained using a CTI/Siemens EXACT ECAT HR+ scanner. Images were acquired using the 3D mode with septa retracted, allowing for 63 slices at an intrinsic resolution of 4.2 mm x 4.2 mm x 4.0mm. The distribution of CBF was measured during a 60 second scanning interval using the $H_2{}^{15}O$ water bolus method (Raichle, Martin, Herscovitch, Mintum, & Markham, 1983). Magnetic resonance imaging scans were obtained with either a Philips ACS III (1.5T) or a Siemens Vision (1.5T) scanner, both producing a high resolution 3D whole brain T1 weighted scan (~140-160 1mm sagittal slices). Each individual's PET and MRI scans were co-registered and linearly transformed into standardized stereotaxic space (Evans et al., 1992; Talairach & Tournoux, 1988). The transformed images were reconstructed using a 14-mm Hanning filter and averaged across subjects. Differences in rCBF were measured by paired image subtraction of the scans of interest. Changes in rCBF were analyzed by dividing the

difference at each voxel by the mean standard deviation of normalized CBF across all intra-cerebral voxels creating a *t*-statistic map (Worsley, Evans, Marrett, & Neelin, 1992). Based on three-dimensional Gaussian random field theory, the threshold for significant *t*-statistic peaks for a total volume size of 182 resolution elements (14x14x14 mm) for grey matter volume of 500 $cm^3$; was set at $t \geq \pm 3.53$. This corresponds to an uncorrected p-value < 0.0004 and a corrected multiple-comparisons false positive rate of 0.58. A directed search was used to examine specific regions where activity had been predicted based on previous findings. For these areas the threshold was lowered to $t = 3.0$. For the conjunction analysis (Price & Friston, 1997), level of significance was set at a conservative *t* value of 3.5 (Worsley & Friston, in press). Anatomical locations of significant *t*-statistic peaks were determined by examining the merged image of the *t*-statistic map with the transformed averaged MRI of all subjects. These locations were compared with the Talairach atlas (Talairach & Tournoux, 1988) and the atlas of Petrides and Pandya (Petrides & Pandya, 1994) to determine the anatomical correlates of the PET activation foci.

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## Chapter Six

## General Discussion

This series of studies of olfactory and visual nonverbal memory has benefited from a carefully planned design, which through the use of parallel tests allowed direct comparisons between patient and PET findings, and between olfactory and visual memory results.

Summary and integration of olfactory and face memory study findings

Hemispheric differences in processing for these two types of nonverbal stimuli were revealed through the investigation of learning and memory in patients with resection from a temporal lobe. Findings from the face memory study showed a deficit restricted to patients with a resection in the right temporal lobe, supporting the predominance of the right hemisphere in memory for faces. Similarly, patients with a right resection also performed poorly on olfactory learning and memory. However, contrary to the findings in the face study (where patients with a left resection performed the same as healthy controls subjects), on the *olfactory* task patients with resection from the left temporal lobe had a level of impairment equivalent to the right resection patients. Hence, the function of the temporal lobe regions is not parallel for these two nonverbal tasks. The right temporal lobe region appears critical for face learning and retention, while olfactory learning seems to call upon both temporal lobes.

The question arises as to why this difference in findings would occur. There is the possibility that face recognition is a truly nonverbal task, but odor memory is not. Although attempts were made to decrease verbal strategies during the olfactory task, perhaps they were not completely successful. However, if patients were able to apply

verbal labels, it would have been those with an intact left hemisphere (i.e. right resection patients) who would have benefited most, yet they were still impaired. Also in the PET study, if subjects were attempting to label the odors during an odor condition, while likely not verbalizing during the no-odorant baseline, activity would be detected in language regions, but this was not the case. Therefore, these findings do not indicate that the participation of the left temporal region in olfactory memory is based on verbal processing, or on language based mechanisms, but rather reflects an odor processing function.

This difference in lateralization between face memory and olfactory memory may be a further manifestation of the differences in the olfactory system compared to other sensory systems. It is known that olfactory cortex is phylogenetically older and that the connections from the receptors to cortical regions are different, and perhaps this finding of substantial bitemporal processing is a reflection of this "older" system. The findings from the PET and patient olfactory studies also strongly indicate that odor memory relies on the participation of both piriform cortices. These results correspond with the findings of Sobel and colleagues (Sobel, Khan, Saltman, Sullivan, & Gabrieli, 1999), which indicated that each nostril detects slightly different odor information, and this information is then sent via ipsilateral pathways to the piriform cortices. This would result in slightly different information being received and encoded in each hemisphere. Hence, it may be that olfactory memory depends on information that is divided between the left and right piriform regions, and that it is the coordinated activity of these two areas that contributes to a more complex and precise memory engram.

Results from the PET face study showed participation of left and right temporal lobe regions in face memory, but there is a clear right hemisphere superiority as indicated by the patient study. In particular, the PET face data revealed greater left temporal activity during encoding than long-term recognition and greater bilateral participation of fusiform regions in long-term face recognition versus encoding and short-term recognition. This suggests that invasion of either left or right temporal lobe regions may invoke impairment in face recognition. However, it is clear from the patient study that a deficit follows resection from the right temporal lobe, but not from resection from the left. It is also apparent that the fusiform face region is rarely invaded in our patients, and this is supported by the adequate face perception of right resection patients: they performed at the same level as healthy subjects on the face discrimination task. Therefore the overall findings would indicate that resection of temporal lobe areas outside of the fusiform, in mesial and more anterior regions, are responsible for the memory deficit.

The comparisons made in the face memory PET study allow for the examination of differences among brain regions for three memory processes. However, regions that are *common* to each memory process would not be detected. Further examination of memory tasks in comparison to a low level baseline task would help to reveal all regions that are participating in face memory. This is the aim of one of my recently designed experiments. By evaluating different stages of memory processing, encoding, short-term and long-term recognition as compared to a simple baseline task, the broad regions that participate to a greater extent in face perception versus memory will be revealed. Then a conjunction analysis could be employed to determine common regions of activity that

occur in all three types of memory processing. The integration of this new information with that of my PET study would expand our understanding of the specific structures active within the temporal lobes in relation to the different aspects of face memory.

Another important facet of the face recognition memory experiments was the sensitivity of the face learning test to right hemisphere function. The test's high level of sensitivity (82%) to right hemisphere dysfunction as well as its high rate of correctly rejecting left resection patients (specificity = 79%) suggests that this test may be clinically useful in neuropsychological assessment. To evaluate this possibility further, a new study has been initiated that will examine the ability of this test to correctly classify unoperated temporal lobe epilepsy patients to left or right seizure focus as determined by EEG and MRI. Previous tests that have shown good rates of classification of groups of patients with surgical lesions have been less successful among patients with less invasive brain damage. Therefore, it is important to determine if this test will also be sensitive to less severe interference in brain function. In order to broaden the scope of this research, patients with seizures arising in the frontal lobes will also be tested. Although this particular patient population tends to be very small, it would be of great interest to determine if patients with right dorsolateral prefrontal dysfunction would be impaired. This result would be predicted based on the PET findings of significant participation of the right dorsolateral prefrontal region during short-term face recognition.

Activity of the dorsolateral prefrontal cortex was also of interest in the PET odor memory study, and examination of the data from the face and olfactory studies showed similar patterns of activity between the short-term and long-term recognition conditions within this region. In both the odor and face PET studies, significant dorsolateral

prefrontal activity was found during short-term recognition as compared to long-term recognition, suggesting a common brain region for this stage of memory processing, independent of the type of material to be remembered. The question arises as to whether the similarities in regions of activity are due to the different stimuli being translated by the subject into the same code, presumably through labelling. However, it is unlikely that this similarity of function during short-term recognition conditions is due to verbalization, as the face task cannot be completed by verbal mediation and the olfactory task was designed to make verbal strategies inefficient. Additional support for similar usage of dorsolateral prefrontal cortex for these two types of mnemonic material came from the working memory study, where PET scans of odor processing and face processing were compared directly to each other. Increased activity in dorsolateral prefrontal cortex was noted during both olfactory and face working memory conditions (as compared to the appropriate sensorimotor control task). Moreover, the two working memory conditions showed several areas of common increased activity within dorsolateral prefrontal areas as determined by conjunction analysis. This further supports the notion that the dorsolateral prefrontal cortex acts as a common processor for all types of material that is to be kept online.

Conclusion

This series of studies examined several aspects of olfactory and face memory that had not been investigated previously. Although there are many studies that have examined human olfaction, my findings contributed to this body of knowledge in several ways: initially, through the development of the first nonverbal odor learning and memory test, and later through the study of odor encoding and long-term memory using functional

brain imaging (an approach that has not been used previously to investigate these processes). The integration of findings from the olfactory studies have led to hypotheses about the requirement of intact bilateral piriform cortices for accurate odor memory processing, as well as furthering the suggestion that the piriform cortex plays an active role in memory processing and is not a purely perceptual processor. Future investigations into the areas of odor familiarity and into specific learning processes will likely shed more light on this interesting possibility.

The examination of face learning also led to important insights into face memory processing, and to a protocol that may prove to have clinical utility in testing face recognition in patients. Interestingly, face learning (with a multiple learning trial paradigm) had not been examined previously. Thus, the creation of the unique testing paradigm used in my studies allowed the first investigation of face learning across multiple exposures. But, more importantly, this test shows promise of being a clinically useful neuropsychological tool in the assessment of right hemisphere function, and current investigations in studies of unoperated epilepsy patients will help to clarify this possibility.

Finally, through the combined investigation of olfactory and visual memory I was able to compare and contrast brain regions involved in different aspects of memory, including working memory for these two modalities. This research also provided the first examination of olfactory working memory. Overall, my system of parallel tests and complementary methodologies yielded important insights into differences in hemispheric lateralization of olfactory and face memory, and teased out smaller regions in the hemispheres that play a specific role during particular stages of memory processing.

Studies that I plan for the future using fMRI will be an exciting means to pursue these findings further, and to investigate in more detail how these regions interact temporally.

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