FUNCTIONAL MAGNETIC RESONANCE IMAGING OF LANGUAGE PROCESSING AND ITS PHARMACOLOGICAL MODULATION

DISSERTATION

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By

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ABSTRACT

Functional Magnetic Resonance Imaging (fMRI), a non-invasive technique extensively employed for mapping brain function, was used to examine brain activation during language processing and the effect of dopaminergic agents on brain hemodynamics and language. Administration of Levo-Dopa, a drug known to increase levels of dopamine in the brain and used to treat Parkinson’s disease, has been associated in behavioral studies with restriction of the semantic network. The current project attempts to identify how these behavioral findings are reflected in brain activation as determined with fMRI. These investigations are summarized in the following.

In the first part of the project, the goal was to determine the effect of L-Dopa on brain hemodynamics. This was motivated by the fact that the fMRI signal is based on cerebral blood flow, oxygenation and cerebral blood volume changes, and any drug administration could interfere with the coupling of neural activation with these parameters, independent of neuronal activity. In order to obtain information about possible global changes in cerebral blood flow (CBF) due to drug administration, a
theoretical model of a relationship between the blood oxygenation level dependent (BOLD) signal and CBF was used. The BOLD signal was measured in two brain regions, motor and visual cortices, in two treatment conditions, placebo and L-Dopa, for each participant. Within subject comparisons revealed no significant differences between the measured BOLD signal in the two conditions, and the calculated changes in baseline CBF were less than 1% for both motor and visual cortices. We concluded that the changes in global CBF due to the drug administration were not significant and as a consequence, this was not used as a covariate in subsequent studies of drug effect on specific cognitive functions.

The second part of the project examined the effect of semantic priming on brain activation, and the modulatory effect of dopamine on this type of language processing. The aims of this part of the project were: to implement a protocol for language function imaging, to explore different types of paradigm design in fMRI, and finally to examine the effect of semantic priming on brain activation and the effect of L-Dopa. Behavioral measurements were recorded and demonstrated a significant priming effect for all semantic distances. Imaging results showed activation in a cerebral network known to be involved in language processing and attention to task, similar to other studies previously reported in literature, thus confirming the successful implementation of our language imaging protocol. Two types of paradigm design, block and event related, were explored and the results were compared. They revealed different patterns of activation emphasizing the importance of careful selection of design in functional neuroimaging studies of cognitive functions. For the pharmacological part of the study a within subject design was used, each participant undergoing two scanning sessions, after ingesting L-
Dopa and placebo. During each testing session, each participant performed two scan runs, targeted to examine automatic versus controlled processing. This way we were able to study both the effect of temporal characteristics of the priming process and the effect of L-Dopa on brain activation. No drug or temporal effects were found on the activation maps, suggesting that more sensitive techniques must be used to detect these changes. Our findings support the network model for the organization of semantic lexicon.

Lastly, fMRI was used to study functional connectivity associated with semantic and phonological processing. The goal was to explore the interaction between language network components and to determine if administration of L-dopa would affect this interaction or these types of language processes. During two test sessions (placebo and L-Dopa) each participant performed two fMRI runs, involving phonological and semantic processing of visually presented words. These were used to generate maps of semantic and phonological networks. Activation patterns for the two language processes were obtained and compared to previous findings. A number of regions of interest (ROI) commonly activated by the two tasks, were chosen based on these activation maps and the functional connectivity was calculated as the degree of correlation between the activation time series data of two brain areas. The functional connectivity analysis revealed that language areas were activated in a more synchronous manner (i.e. higher correlation coefficients) for phonological tasks than for semantic tasks. No drug effect was found on either the activation maps or the functional connectivity results. Our findings could be of significance for patient populations showing atypical levels of dopamine in their brain, such as cocaine withdrawal, Parkinson’s disease or schizophrenic patients.
Dedicated to my husband, Cristian
I would like to begin by thanking my advisors Dr David Beversdorf and Dr. Petra Schmalbrock. Dr. Beversdorf offered me the opportunity to work on these projects, and I greatly appreciate his enthusiasm and support. I am grateful for Dr. Schamalbrock’s guidance and expertise, for her constant help and appreciation from the beginning of my research experience at the Ohio State University.

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VITA

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CHAPTER 1

INTRODUCTION

Functional Magnetic Resonance Imaging (fMRI) is a non-invasive technique extensively used for mapping brain function, in order to understand the anatomical substrates of human functions and behavior. This technique was employed in the present project to examine the effect of dopaminergic agents on brain hemodynamics and language processing. Levodopa/carbidopa (L-Dopa), a drug known to increase the levels of dopamine in the brain and to affect language processing was used to assess these effects.

The role of dopamine in the central nervous system is both that of a neurotransmitter and a non-specific neuromodulator. Dopamine affects brain processes that control movement, emotional response, and ability to experience pleasure and pain. Disrupted dopamine flow can cause motor rigidity, incoherent thought, an overly suspicious personality, poor social interaction, as well as problems with working memory. The neuromodulatory function of dopamine has been associated with the signal-
to-noise ratio in cortical networks. It is believed that catecholamines amplify strong signals and attenuate background noise, therefore increasing the signal-to-noise ratio of cortical information processing. This should also be reflected in the effect of increased levels of dopamine on language processing: a more focused activation in the semantic network, and therefore more difficult access to more distant nodes in the network. This effect has been demonstrated in behavioral studies on both healthy individuals to whom the drug was administered, and in patient populations such as schizophrenics, who have abnormally high levels of brain dopamine. The current project attempts to identify how these behavioral findings are reflected in brain activation as determined with fMRI. This work consists of three different sub-projects, presented in detail below.

Since the fMRI signal is based on cerebral blood flow, oxygenation and cerebral blood volume changes, drug administration could interfere with the coupling of neural activation with these parameters, independent of neuronal activity. Therefore the first study in this project tried to determine if L-Dopa administration has an effect on brain hemodynamics. In order to obtain information about cerebral blood flow (CBF) and possible changes of this parameter due to drug effect, a theoretical model reflecting a direct relationship between the blood oxygenation level dependent (BOLD) signal and CBF was used. The average BOLD signal during a combined motor and visual task, extracted from two regions of interest, motor and visual cortex was used to determine the corresponding CBF changes, which were then compared between drug conditions.

The second part of the project examined the effect of semantic priming on brain activation and the modulatory effect of dopamine on this type of language processing. Semantic priming is defined as the facilitation of the response to a target word when it
follows a semantically related prime. Different levels of association between the prime
and target word can yield differential semantic priming effects. We studied this process
with fMRI in order to establish how it affects the spread and magnitude of brain
activation during a lexical decision experiment. This was done in two stages: firstly a
pilot study, using a block design was performed in normal controls. The goal of this pilot
study was to develop a language imaging protocol at The Ohio State University and to
determine if fMRI can detect different levels of semantic priming. Previous research has
demonstrated a modulation of brain activity in language areas in the context of semantic
priming, but the effect of varying semantic distances has not been studied. This study
therefore examined the graduated effect of three varying semantic distances on cerebral
activation. Considering the results of this pilot study, an event related design was
subsequently used to better assess the effect of semantic priming on brain activation. A
within subject design was used, each participant undergoing two scanning sessions, one
each after ingesting L-Dopa and placebo. During each testing session, each participant
performed two scan runs, targeted to examine the automatic versus controlled processing.
This way we were able to study both the effect of temporal characteristics of the priming
process and the effect of L-Dopa on brain activation.

Finally, fMRI was used to study functional connectivity associated with semantic
and phonological processing. Since administration of L-dopa has been shown to result in
restricted semantic networks, we wanted to explore whether this also affects the
interaction between language network components, as revealed by functional
connectivity. Functional connectivity is calculated as the degree of correlation between
the activation time series data of two brain areas. During two test sessions (placebo and
L-Dopa) each participant performed two fMRI runs, involving phonological and semantic processing of visually presented words. These were used to generate maps of semantic and phonological networks. A number of regions of interest (ROI) commonly activated by the two tasks were chosen based on these activation maps and functional connectivity was calculated and further analyzed for effects of either the drug or task.

Background information as well as the methods and experimental results of our work are presented in the following chapters:

Chapter 2 is the Background chapter and covers several topics important for the current project. It begins in sub-chapter 2.1 with a short review of the fMRI technique, with emphasis on brain physiology and changes in brain hemodynamics. The effects of using pharmacological agents on these parameters are then reviewed, in order to establish the significance of careful control of studies involving drug effects on specific brain functions. Also, the paradigm design and its importance in fMRI studies is presented, differentiating the advantages as well as the drawbacks of both block and event related designs. Finally, a brief description of functional connectivity as used in the current project is given, and its significance for characterizing central nervous system operation is presented.

Section 2.2 is dedicated to the description of the language system in the brain, as determined through behavioral, lesion and neuroimaging studies, with emphasis on the specific language processes studied in the current experiments: semantic priming as well as other semantic and phonological processes.

Section 2.3 deals with the catecholamine systems, beginning with a description of L-Dopa biochemistry. Since L-Dopa can convert to both dopamine and norepinephrine,
description of dopaminergic and noradrenergic systems is in order. A review of the current knowledge of the effects of L-Dopa on language processing is also included in this section.

In Chapter 3 we describe in detail our experimental methods, including the selection criteria and other characteristics of the human participants in these studies, a detailed description of the experimental set-up used as well as the fMRI paradigm design for each sub-project. A description of the imaging protocols and a detailed description of the data analysis used are also included in this chapter.

The goal of Chapter 4 is to present the results for each sub-project and to discuss the implications of these results.

Finally, Chapter 5 contains the general conclusions of this work and presents possible future work needed to complete and strengthen the current findings.

In summary, the specific aims of the dissertation are to:

1. Characterize the effect of L-Dopa/carbidopa on brain hemodynamics.
2. Utilize fMRI as a tool to determine the effect of semantic priming on brain activation and to assess dopaminergic modulation of semantic priming.
3. Use fMRI as a tool to determine brain functional connectivity during language processing and the effect of L-Dopa on it.
CHAPTER 2

BACKGROUND

2.1. Functional Magnetic Resonance Imaging (FMRI)

The understanding of the functional organization of the human brain has been the main quest of neuroscientists for over a century. Until recently the study of brain function was based on either postmortem studies of lesions in the brain, cortical stimulation of patients undergoing surgery, electrode measurements on animals and subsequently anatomical imaging. In the past 15 years the brain imaging techniques have evolved to allow the study of healthy human subjects.

Using substances labeled with radioactive isotopes, positron emission tomography (PET) became the first useful technique that allowed production of functional maps of the brain. In 1990 the first experiment using magnetic resonance imaging (MRI) to study brain function was performed\textsuperscript{1}. The main advantage of functional MRI (fMRI) over PET is that it is a non-invasive technique while PET requires intravenous injection of a radioactive isotope. Unlike PET, which measures blood flow directly, MRI measures blood flow indirectly by detecting magnetic susceptibility changes associated with the
relative concentration of oxy- and deoxy-hemoglobin in brain vessels. The different magnetic properties of the blood in the two states (oxygenated and deoxygenated) provide the contrast in the fMRI images: if blood oxygenation increases the local MR signal also increases. This effect, called Blood Oxygenation Level Dependent (BOLD) contrast, is the basis of most of the fMRI studies of brain activation performed today.

2.1.1. Brain physiology and functional MRI

Energy metabolism in the brain is necessary not only for the basic processes of cellular work but also for the generation of electrical activity required for neuronal activation\(^2\). The connection between neural activity and energy metabolism is the basis of functional neuroimaging.

A significant amount of free energy is required in order to sustain neuronal signaling as well as to maintain the resting electrical and chemical equilibrium. The common energy currency in the brain is ATP, and in order to restore its resource of ATP the working brain requires a continuous supply of glucose and oxygen. This is accomplished by cerebral blood flow (CBF), which therefore varies with neural activity\(^3,4\). Changes in CBF are accomplished by changes in cerebrovascular resistance and therefore changes in cerebral blood volume (CBV).

For functional brain imaging, the desirable signal changes are those caused by neuronal activity. However, the electrical activity itself is not detectable using MRI. Instead, the above mentioned changes in local blood flow, volume and oxygen consumption that accompany neural activity determine a change in the concentration of oxygenated and deoxygenated blood. These hemodynamic effects occur within a few
seconds of changes in neural activity. Hemoglobin, in its two states has different magnetic properties: oxygenated hemoglobin is diamagnetic while deoxygenated hemoglobin is paramagnetic. As a result, a change in the oxygenation of hemoglobin leads to changes in the microscopic distribution of local magnetic fields thus influencing the MRI signal\textsuperscript{3,4}. The changes in physiology that affect the MR signal and make neuronal activity detectable by fMRI can be summarized as follows: following increased demand of energy due to neuronal signaling, the cerebral blood flow, blood volume and oxygen consumption increase. The cerebral metabolic consumption of oxygen (CMRO\textsubscript{2}) does not increase at the same rate as the blood flow and volume; therefore, there will be an oversupply of oxygenated blood, resulting in a lower concentration of deoxy-hemoglobin in the veins. The effect of this phenomenon, also known as neuro-vascular decoupling, is an increase of the T\textsubscript{2} and T\textsubscript{2}* relaxation times and of course of the MR signal in the vicinity of the veins downstream from the activated tissue. This effect provides the BOLD contrast for the MRI images\textsuperscript{3,4,5}.

2.1.2. Cerebral blood flow and metabolism coupling and BOLD signal

The BOLD signal is as a representation of complex metabolic changes and coupling of oxidative metabolism to glucose consumption and blood flow, both of which increase dramatically with task activation. Oxidative metabolism is a significant component of the metabolic response of the brain to functionally induced changes in cellular activity\textsuperscript{3,4,5,6}. Cerebral blood volume has also an effect on the BOLD signal, although the contribution of changes in arterial, capillary or venous blood volumes is still controversial. One hypothesis\textsuperscript{3} is that the dilation of the venules caused by increased
blood pressure in the veins due to lowering of arteriolar resistance may constitute relevant changes in CBV affecting the magnetic resonance signal. The arteriolar dilation which regulates CBF is likely to have a minor influence on BOLD, because the arterial blood is a small fraction of total blood volume (<5%) and its dHb concentration is insignificant.

The magnitude of the BOLD signal is dependent on the relationship between changes, if any, in CMRO and the changes in CBF. The greater the increase in CMRO for any increase in CBF, the smaller the BOLD signal becomes and vice versa.

The BOLD effect behaves as a change in observed NMR transverse relaxation rate, $\Delta R^*$:

$$S = S_0 e^{-TE R^*_2} \quad (2.1)$$

$$BOLD = \frac{S_a - S_r}{S_r} = \frac{S_a}{S_r} - 1 = \frac{e^{-TE R^*_2a}}{e^{-TE R^*_2r}} - 1 = e^{-TE \Delta R^*_2} - 1 \quad (2.2)$$

where $S_0$ - baseline MR signal

$S_a$ - MR signal during active state

$S_r$ - MR signal during rest state.

For the remainder of this chapter, the indices $a$ and $r$ indicate respectively active and resting state.
For the small changes in $R_2^*$ that occur during fMRI the exponential function can be linearized (using Taylor expansion $e^x \approx 1 + x$ for $x << 1$) resulting in a simplified expression:

$$BOLD \cong -TE \cdot \Delta R_2^* \quad (2.3)$$

The relaxation rate depends on the static magnetic field, oxygenation level and regional cerebral blood volume according to a validated semi-empirical expression that is now commonly used:\(^3\):

$$R_2^* = K \cdot (1 - Y)^\beta \cdot rCBV \quad (2.4)$$

where: $K = \frac{4}{3} \pi \gamma \Delta \chi_B B_0$

$\gamma$ - gyromagnetic ratio for protons (42.58 MHz/T at $B_0=1.5$T)

$\Delta \chi_B$ - susceptibility difference between oxygenated and deoxygenated blood

($\Delta \chi_B=0.8 \times 10^{-7}$ for blood with hematocrit (Hct) level of 0.4)

$B_0$ static magnetic field (1.5T)

$Y$ - fractional oxygenation level

$rCBV$ - regional cerebral blood volume

$\beta$ is a constant\(^3,6,9\) in the range $1 \leq \beta \leq 2$. 

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Stimulus independent relationship between CBF and CBV is given by the commonly used and verified Grubb’s formula. This was initially determined through in vivo studies in rhesus monkeys, by employing a technique using radioactive $^{15}$O-labeled carboxyhemoglobin and water$^7$:

$$\frac{rCBV_a}{rCBV_r} = \left(\frac{CBF_a}{CBF_r}\right)^\alpha \quad (2.5)$$

where $\alpha=0.38$.

The conservation of oxygen delivery and oxygen uptake is described by Fick's law. This states the mass-balance principle that oxygen delivery is proportional both to blood flow (CBF) and to the arteriovenous oxygen$^8$:

$$CMRO_2 = OEF \cdot CBF \cdot C_a \quad (2.6)$$

where: OEF- tissue oxygen extraction fraction$^{3,5}$; OEF=1-Y and $C_a$- arterial oxygen concentration.

Furthermore, Fick’s law can be written as:

$$CMRO_2 = C \cdot CBF \cdot Hct \cdot (1-Y) \quad (2.7)$$

where: $C$- constant related to the oxygen carrying capacity of hemoglobin

Hct (hematocrit) - fraction of blood volume occupied by red blood cells.
Plugging in eq. (2.5), (2.6) and (2.7) into eq. (2.4) and then into eq. (2.3) (for detailed calculations see APPENDIX A), the BOLD signal complex dependence on the regional blood flow, blood volume and oxygen consumption is given by \(^3,6,9\):

\[
BOLD = K \cdot TE \cdot rCBV_r (1 - Y_r)^\beta \left[ 1 - \left( \frac{CMRO_{2a}}{CMRO_{2r}} \right)^\beta \left( \frac{CBF_a}{CBF_r} \right)^{\alpha - \frac{1}{\beta}} \right] (2.8)
\]

where: 
\( K = \frac{4}{3} \pi \Delta \chi_{ab} B_0 \cdot \) and \( M = K \cdot TE \cdot rCBV_r (1 - Y_r)^\beta \).

Hoge et al. and Davis et al.\(^6,9\) showed that different \( \beta \) values (in the range \( 1 \leq \beta \leq 2 \)) would change their results only by 2-4%, which is of the order of their standard error of measurement for a single subject. Therefore in the following \( \beta = 1 \) is assumed. Fig. 2.1 is a graphical representation of this relationship\(^9\), extensively used to describe the relationship between BOLD signal and physiological parameters.

\[
BOLD = M_{\beta=1} \left[ 1 - \frac{CMRO_{2a}}{CMRO_{2r}} \left( \frac{CBF_a}{CBF_r} \right)^{\alpha - 1} \right] (2.9)
\]

where \( M_{\beta=1} = K \cdot TE \cdot rCBV_r (1 - Y_r) \).
2.1.3. Pharmacological fMRI

Pharmacological fMRI refers to the use of MRI to study drug effects on central nervous system functions. This can be done either directly, using centrally acting drugs, or indirectly by using peripherally acting drugs. This technique can provide information about the sites and mechanisms of the drug. Also, different drugs can be used as a tool to better understand certain brain functions. More specifically, granted that careful control of the design has been accomplished, pharmacological fMRI can be used to: determine specific target sites for the drug, study the temporal characteristics of drug action as well
as the magnitude of the drug effect, examine dose response results, observe sensitization (enhanced drug effect due to repeated administration) and tolerance effects (decreased drug action due to repeated administration), study the effect of chronic drug administration on brain function as well as of the withdrawal from drug use\textsuperscript{5,10}. There are two types of studies aiming to determine the effect of drug on the fMRI signal\textsuperscript{10}: 1) studies of acute drug administration, when an fMRI baseline acquisition is performed during a placebo followed by a drug infusion; 2) an activation paradigm, targeting a specific brain function is acquired separately during respectively drug and placebo administration. Our goal was to study the effect of a drug on specific cognitive functions; therefore the second category of pharmacological studies, employing an activation paradigm, will be the focus of the subsequent discussion.

The use of pharmacological agents with fMRI entails additional precautions. There has to be additional screening of participants and more careful monitoring of the subjects has to be performed, since either the drug or the MRI environment can exacerbate feelings of anxiety and worries related to the procedure. Close physiological monitoring is also necessary, both for participant safety as well as for proper fMRI data interpretation.

The most important issue in pharmacological fMRI is the possible effect of the drug on global brain hemodynamics. Since the fMRI signal is not a direct measure of neuronal activity, but is based on blood flow, oxygenation and blood volume changes, one has to take into account the possibility of a specific drug affecting these parameters globally. If a drug has an effect on the hemodynamic response, this effect must be either
included or removed from the interpretation of specific drug effects on areas of
activation. Some strategies that can be used in order to accomplish this are:

- determination of BOLD changes during rest/baseline condition, with and
  without drug
- incorporation of a control task to determine non-specific drug effects on
  activation
- use of specialized imaging pulse sequences to determine general blood flow
  (arterial spin labeling sequences) and blood volume (use of contrast agents)
  changes due to drug.

The control method of choice depends on the type of drug studied. There have
been various studies involving some pharmacological agents: cocaine, nicotine, ethanol,
methylphenidate, sulpiride, diazepam, scopolamine, L-Dopa, etc. both in humans and
animals\textsuperscript{11-18}. For example, cocaine dramatically affects the cerebral blood flow due to a
vasoconstriction of both coronary and cerebral vessels in humans exposed chronically to
the action of cocaine\textsuperscript{18-20}. Therefore, determination of baseline changes in blood flow and
volume is important before determining changes induced by more complex tasks. The use
of a CBF sensitive imaging sequence\textsuperscript{21} followed by a BOLD sequence could accomplish
this, as Gollub and colleagues demonstrated in an acute cocaine administration fMRI
study\textsuperscript{11}. In other cases it is enough to include a control paradigm that activates a brain
area that does not bind the specific drug\textsuperscript{10}. For example, Seifritz and colleagues\textsuperscript{13} have
chosen to estimate the hemodynamic contribution of ethanol to the BOLD effect, by
modeling a relationship between the regional blood flow and BOLD signal changes. Such
an approach is presented in detail in the following section.
2.1.4. Modeling drug induced changes in baseline CBF from BOLD signal

As previously mentioned, intake of commonly used substances (caffeine, nicotine, alcohol) as well as various drugs (both recreational and therapeutic) is known to cause global perturbations in CBF. Therefore, when studies involving administration of such substances are performed, it is important to examine/determine if there are any global changes in baseline CBF and how these affect the BOLD signal of interest.

The question of how global changes in CBF affect local BOLD changes is still controversial. There are two suggested models that describe these changes:

a) Some findings suggest that local CBF changes induced by stimulation are proportional to the basal global CBF. Therefore if there is an increase of the baseline CBF, there will be a proportional increase in the active state flow, resulting in a constant relative change of regional CBF\textsuperscript{11,22,27}. Therefore the local BOLD response, expressed as percent signal change, should not be affected by changes in baseline global CBF\textsuperscript{11,22,27} (see Fig 2.2 a)).

b) However, more studies\textsuperscript{13, 23-26, 28-30} seem to confirm the second model. This model suggests that the local absolute value of blood flow during active state is independent of the baseline CBF, i.e. it will be the same for the same stimulus, no matter what the baseline flow is. This means that, for increased baseline CBF and constant active state CBF, the difference in blood flow between active and rest state will decrease when compared to normal baseline flow. This will also result in a reduced BOLD signal\textsuperscript{13, 23-26,28-30} (see Fig 2.2 b)).
Fig 2.2: BOLD signal changes associated with normal and increased global baseline CBF: BOLD$_N$ is the signal change at normal global CBF; BOLD$_{IB}$ is the signal change when the global baseline CBF is increased from the normal state. a) Model that assumes active state CBF values are proportional with the baseline CBF, therefore BOLD$_N$=BOLD$_{IB}$; b) Model that assumes active state CBF values are independent on the baseline CBF, therefore BOLD$_N$>BOLD$_{IB}$ for increased baseline CBF.

Considering the latter theory, assuming that global perturbations in CBF affect the BOLD signal of interest, changes in basal CBF result in changes in baseline signal, and no changes in active state signal (i.e. rCBV$_a^D$=rCBV$_a^P$; CBF$_a^D$=CBF$_a^P$ and Y$_a^D$=Y$_a^P$), therefore$^{13,28,30}$:

$$R_{2a}^D = R_{2a}^P$$

(2.10)

where D-drug, P-placebo.
From eq (2.4) and (2.10):

$$(1 - Y_a^D) \cdot rCBV_a^D = (1 - Y_a^P) \cdot rCBV_a^P$$  \(2.11\)

Let’s assume \(\Omega\) is the percent increase in baseline CBF in drug condition (relative to the placebo condition):

$$\Omega = \frac{CBF_r^D - CBF_r^P}{CBF_r^P}$$  \(2.12\)

then

$$(1 - Y_r^D) = \frac{(1 - Y_r^P)}{(1 + \Omega)}$$  \(2.13\)

From Grubb’s law (eq. (2.5)) and eq. (2.13) results:

$$rCBV_r^D = rCBV_r^P \cdot (1 + \Omega)^\alpha$$  \(2.14\)

Plugging eq. (2.11), (2.12), (2.13), (2.14) into eq. (2.9) (for detailed calculations see APPENDIX B), the estimated reduction in BOLD signal change as function of increased baseline flow due to drug administration is given by:

$$\frac{BOLD_r^D}{BOLD_r^P} = \frac{(1 + \Omega)^{\alpha - 1} \cdot (1 - Y_a^P) \cdot rCBV_a^P}{(1 - Y_r^P) \cdot rCBV_r^P}$$  \(2.15\)
Using experimentally determined numerical values from literature \((Y_r=0.75, \ Y_a=0.88, \ r_{CBV}=0.049, \ r_{CBV}=0.062)^{13}\), for the fractional oxygenation level and cerebral blood volume in the active and rest state un-affected by drug, this complex formula reduces to:

\[
\frac{BOLD^D}{BOLD^P} = 2.55(1 + \Omega)^{-0.62} - 1.55 \quad (2.16)
\]

which is represented graphically in Fig 2.3.

To obtain a direct relationship between BOLD signal and CBF changes, eq. (2.12) can be used, and so eq. (2.16) becomes:

\[
\Omega = \frac{CBF_r^D - CBF_r^P}{CBF_r^P} = \left(0.39 \frac{BOLD^D}{BOLD^P} + 0.61\right)^{-1.61} - 1 \quad (2.17)
\]

represented graphically in Fig.2.4.

This equation can be used to estimate drug-induced changes in baseline CBF from a measured BOLD signal.
Fig. 2.3: BOLD changes are dependent on drug related baseline CBF changes (Eq. 2.16).

Fig 2.4: Drug induced changes in baseline flow (Eq. 2.17).
2.1.5. Paradigm design: block design vs. event related design

One of the most important issues that need to be addressed when performing an fMRI study is the choice of paradigm design. This is driven by the questions that need to be answered by a particular experiment (specific cognitive function that the experimenter is interested in) as well as methodological limitations, such as the temporal characteristics of the BOLD signal and the possibility of processing data collected with a particular design.

Some of the issues that have to be considered when selecting a paradigm design are the sensitivity and linearity of the BOLD signal as well as the sampling rate.

It has been demonstrated experimentally that the BOLD signal is sensitive to stimuli as brief as 100ms (Fig. 2.5) or even shorter depending on the brain area being examined: a response to visual stimulation as short as 34ms has been detected (for a review see Jezzard\textsuperscript{4}).

Another feature of the BOLD signal important for the design and analysis of an experiment is the linearity of the signal. The hemodynamic response to stimulation is predictable and relatively reproducible across events, even when these overlap. Moreover the hemodynamic responses for individual events add in an approximately linear fashion\textsuperscript{4,33}. This is presented in Fig. 2.6, reproduced from a study examining visual stimulation presented as fast as 2s apart. However, at faster rates there may be a departure from linearity, for which the cause is still unknown\textsuperscript{4}.
Fig. 2.5: Brief visual stimuli, lasting 34, 100 and 1000ms can be detected with fMRI (reproduced from Ref 4).

Fig 2.6: The hemodynamic response function to 1s visual stimuli presented every 2s. A: Raw data from one-, two-, and three-trial clusters reveal a larger response as the number of trials increases. B: The estimated contribution for each event: suggesting that the hemodynamic response added in a roughly linear fashion (reproduced from Ref 33).
It is important for fMRI experiments that the signal is acquired very fast, so that whole brain coverage and sufficient statistical power can be achieved. While the actual sampling rate is determined by the repetition time TR, which is limited by hardware capabilities, shorter effective sampling rate can be obtained by decoupling the timing of the stimulus presentation and the timing of image acquisition. If the temporal relationship between data acquisition and stimulus presentation is fixed there may be a bias in both the amplitude and location of the estimated activation. The solution to this problem is to use distributed sampling. Distributed sampling is ensured if the inter-stimulus time and TR are not integer multiples of one another. Fig 2.7 shows simulations by Price et al. meant to demonstrate how using distributed versus fixed sampling influences the amplitude of the BOLD signal in a block design. During fixed sampling (filled circles in Fig. 2.7) the fit of the model to the data in slice 1 underestimates the response while in slice 2 it overestimates it, while in the case of distributed sampling (open circles in Fig. 2.7) the response is less biased. Fig. 2.8 presents the experimental finding of brain activation in a language task, when the two types of sampling are used. Additional activated regions (indicated by the blue arrows) are shown during distributed sampling designs, which do not appear as active in the fixed sampling design.
Fig 2.7: Simulated hemodynamic response during a block design fMRI experiment: the thin line represents the actual signal, the thick line represents the estimated hemodynamic response (reproduced from Ref 34).
There are two main classes of fMRI paradigms: the block design in which the stimuli are clustered together in blocks of length between 15 to 60 seconds, to allow the appearance of continuous activation during the block; and the event related design where responses to individual neural events are examined.

**Block design**

The most common paradigm design used in fMRI experiments is the block design, where a cluster of stimuli are presented continuously during a period of time, followed by a baseline of comparable length. The hemodynamic responses acquired during one blocked condition are compared to the signals acquired from baseline or
signals from other blocks involving different task conditions. A schematic of such a
design and the estimated BOLD response is presented in Fig. 2.9.

![Diagram of block design with 2 experimental conditions: A and B.]

Some of the advantages of block designs are: simplicity: a simple block design is adequate for many types of experiments; good statistical power: a large number of stimuli can be presented quickly during a block; they are easy to analyze: data collected during performance of one task can be clearly separated from that collected during other tasks. However there are also drawbacks to using a block design: it can be predictable and boring potentially leading to attention problems; it is prone to potential confounds such
as: rapid habituation, anticipation, strategy effects; it may be difficult to control a specific
cognitive state for the long periods of each block; a “rest” state is rarely true rest (mind
may wander, subjects want to figure out hypothesis, etc.); it is inappropriate for cognitive
tasks where a reaction to an unexpected stimulus is probed (oddball paradigm, semantic
priming); the BOLD signal may not remain constant across the epoch of interest (e.g. in
pain studies a decrease in BOLD signal is observed after a few epochs); it is not possible
to distinguish individual responses. Some of these issues can be solved by employing an
event related design.

**Event related design**

The event related (ER) paradigms allow for measurement of brain response to
individual stimuli. A picture of such a design is presented in Fig. 2.10. These types of
design are similar to the format of a behavioral study: stimulus events are presented one
at a time, usually in a randomized fashion\(^3\,33,38,39\).

However there are some problems that one has to consider when using this
design: the long duration of the BOLD hemodynamic response, and the fact that the
responses to brief events are weaker than responses to blocks of events, therefore either a
higher field or an increased number of stimuli need to be used. Nevertheless, there are
important advantages of ER designs: 1) they allow for various stimulus events to be
presented randomly in one run; 2) signals from individual trial events, similar to
behavioral and event related potential (ERP) studies can be detected; 3) they allow for
greater flexibility and randomization than block design, leading to less predictable
experiments for the participants; 4) it is possible to estimate the hemodynamic response

function from a single event type by averaging data acquired after many discrete events; 5) they allow one to determine responses to novel or aperiodically presented stimuli, to explore changes over time or specific task components; 6) they allow for self-paced tasks; 7) post-hoc sorting of stimulus trials according to criteria such as correct vs. incorrect responses, remembered versus forgotten items, quick vs. slow response times, etc., can be accomplished.

Fig. 2.10: Example of an event related (ER) design: schematic hemodynamic responses to 3 different individual stimuli A, B and C can be determined.

Some of the drawbacks of ER designs are: design and statistical measures are
more complex than those of block design; the signal to noise ratio (SNR) is lower than for block design (for block design, the percent signal change may be in the range of 3% to 5% while for event-related design, it may be less than 1%). To compensate for this loss in statistical power, the number of trials per condition should be increased and this results in longer scanning times.

The ER designs can be classified based on the time between stimulus trials (inter trial interval=ITI). There are slow ER designs where individual trials are spaced far apart in time to prevent overlap of the hemodynamic functions\textsuperscript{40,41}, and fast ER designs where individual events are closely spaced (ITI may be set to as little as 2 sec)\textsuperscript{42}. The latter can also be classified in ER with fixed ITI and with randomized ITI. Some examples for each of these are presented in Fig 2.11, 2.12, 2.13, 2.14.

In the case of slow ER designs (Fig. 2.11) the hemodynamic response that results from a single trial is allowed to rise and fall completely before the next trial begins. These are easy to analyze, but the long rest periods between stimulus presentations allow for habituation, expectation, and boredom. They also require a very long scan time.

The rapid ER designs (Fig. 2.12) allow more stimuli to be presented for a given scanning time, therefore they are more efficient than slow ER. However because of the closely spaced trials there is an overlap of hemodynamic response function (HRF) and the raw signal is un-interpretable. Statistical processing can be used to deconvolve the signal, which is more or less successful depending on the type of design. The estimation of hemodynamic responses to stimuli presented rapidly can be considered in terms of a set of linear equations\textsuperscript{35}, which can be uniquely solved if there are as many equations as there are unknowns. At every time point, the hemodynamic response can be written as a
sum of responses from different stimuli plus noise. In the case of rapid ER designs with fixed ITI, non-randomized stimulus presentation (Fig 2.12) leads to "multicollinearity". This means that the responses to individual events always overlap in the same way, and as a result it is hard to determine the source of the response (i.e. is the observed hemodynamic response at one time point due to stimulus A alone, or due to stimulus B alone, or stimulus C alone, or is it a combination of these?). Mathematically it is impossible to determine the contribution of individual stimulus to the sum of the hemodynamic responses (i.e. the equations are repetitive and therefore there are less equations than the number of unknowns). Therefore the stimuli must be properly counterbalanced to ensure that each trial type is preceded and followed by each trial type equally often (Fig 2.13). This way every possible combination of trial sequences can be achieved and the overlapping hemodynamic response function can be successfully de-convolved (there will be sufficient equations for the number of the unknowns). The most efficient ER design is the one in which both the stimuli and the ITIs are randomized (Fig. 2.14). In this case a differential ITI results in an even more differential HRF overlap, and although this is more challenging to analyze this design increases the variance in the data set, and provides more information (more equations) from which to derive estimates of the BOLD response$^{35,42}$. 

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Fig. 2.11: Slow ER design with fixed ITI.

Fig. 2.12: Rapid ER with fixed ITI and non-random events.
Fig. 2.13: Rapid ER with fixed ITI and random events.

Fig. 2.14: Rapid ER with ‘jittered’ ITI and random events.
There are different methods to analyze ER fMRI data, from the selective averaging method proposed by Dale and Buckner\textsuperscript{33}, which can be used in the case of slow ER designs, to more complex linear deconvolution methods\textsuperscript{43} used for rapid ER designs. The General Linear Model (GLM), which is the statistical method most commonly used to analyze block designs, can also be employed for the analysis of jittered ER designs. GLM requires that an explicit model is generated of the effects thought to contribute to variability in a data set\textsuperscript{35,44}. These effects can be modeled to account for each type of trial:

\begin{equation}
Y(t) = \beta_1 X_1(t) + \beta_2 X_2(t) + \mu + \varepsilon(t)
\end{equation}

where
- $\beta$-parameter estimate for $X(t)$
- $X_i(t)$ model for stimulus $i$
- $\mu$- constant
- $\varepsilon(t)$- error in model fitting

\subsection*{2.1.6. Functional connectivity in the brain determined with fMRI}

The brain is a network of connection between different areas, formed locally through fibers in the gray matter, where the signal travels at low speed (1m/s), and over long distances through white matter tracts, where the signal travels at 100m/s\textsuperscript{5}. Areas processing similar types of information are in general anatomically connected to each other: cortical columns in the visual cortex, processing similar information (e.g. same
orientation) are interconnected, posterior and anterior language areas are connected, and the motor network involves connections between primary motor cortex and subcortical structures such as basal ganglia, cerebellum and thalamus. Complex cognitive functions and behaviors are mediated by interconnected neural networks. These anatomical connections can be characterized by using diffusion weighted imaging. More complex and difficult to identify are the functional connections. Functional brain images reveal patterns of activation in a spatially distributed network that could reflect neuronal connectivity.

One approach to assess how brain regions are functionally connected is to study the resting brain. EPI images of brain from subjects in “resting” state have shown correlated low frequency fluctuations (<0.08Hz), in several regions of the cortex suggesting functional connectivity between related brain areas. These uncontrolled fluctuations are clearly differentiated from task specific fluctuations of high frequency noise fluctuations (such as cardiac and respiratory). Most of these resting state functional connectivity studies have concentrated on primary motor and sensory networks, but the cingulate cortex system and language network have also been studied.

Such studies can be biased since there is no such thing as a “true resting state”. Even though it is easy to refrain from motor activity, it is almost impossible to cancel all cognitive and sensory events. Therefore uncontrollable events can alter the findings of cross-correlation analysis of low frequency fluctuations. An alternative is to use this type of analysis for task-related activation data sets.

In functional MRI, the connectivity between specialized areas of the brain has been considered to be mediated by functional and effective connectivity. Functional
connectivity has been defined as the “temporal correlation between spatially remote neurophysiological events”\(^4^6\). In neuroimaging, functional connectivity offers indirect evidence of communication or collaboration between areas of the brain but offers “no insight into how these correlations are mediated”\(^4^6\). Such methodology has been successfully applied to study motor, visual and auditory systems\(^5^1\), visual delayed recognition task\(^5^2\), sentence comprehension and working memory in high functioning autism\(^5^3, ^5^4\). Effective connectivity has been defined as “the influence one neuronal system exerts over another”\(^4^6\). Effective connectivity is closer to the anatomical connectivity, and is a statistical model of the influence one neuronal system has over another\(^4^6\). The following section will only focus on discussing the functional connectivity.

Functional connectivity is calculated by extracting time series from brain regions of interest, after all the pre-processing steps (motion correction, filtering of high-frequency noise, etc.) have been performed. Then correlation coefficients (cc) are calculated between the time series of two regions of interest using eq. (2.19), in order to determine if they are functionally connected\(^5^1\).

\[
cc = \frac{\sum_{i=1}^{N} (x_i - \mu_x)(y_i - \mu_y)}{\sqrt{\sum_{i=1}^{N} (x_i - \mu_x)^2 \sum_{i=1}^{N} (y_i - \mu_y)^2}}
\] (2.19)

where

- \(x_i\) and \(y_i\) are the two time courses in vector form that denote the signal at time \(i\), from voxels (ROI) \(x\) and \(y\) in the brain;
- $\mu_x$ and $\mu_y$ are the average values of vectors $x$ and $y$.

Functional connectivity is an important aspect in characterizing central nervous system operation. It helps to identify better how the brain is organized functionally and how this organization changes with disease or is modulated by drug action.

### 2.2. Language

Language is a system of communication that allows us to express and understand ideas. All languages are based on similar principles and develop spontaneously in children. The basic units of language are words, arbitrary associations between sounds or symbols and meaning. The combination of these units into bigger words, phrases and sentences following certain rules constitutes grammar\(^2,55\). To comprehend and produce language a complex stream of information connecting different parts of the brain is required and will be described in the following section.

#### 2.2.1. Neuroanatomy of language system

About 96% of the population depends on the left hemisphere of the brain for language processing but the right hemisphere also contributes especially for the emotional and pragmatic aspects of language.

Initial studies of neuroanatomical localization of language were based on the study of brain lesions. According to initial understanding from these lesion studies\(^2\), presented in Fig. 2.15, the principal areas of the brain involved in language are: Wernicke’s area responsible for understanding language, Broca’s area, responsible for the
production of language and the arcuate fasciculus, a unidirectional pathway of
information from Wernicke’s area to Broca’s area.

In line with this model, the anatomy of heard word repetition would involve the
primary auditory cortex for acoustic processing, a connection to Wernicke’s area and
then to Broca’s area, while speech generation would be accomplished through the motor
area. Similarly for read word repetition, the primary visual cortex processes visual
information, then there will be a connection to the angular gyrus, then a connection to the
Wernicke’s area, Broca’s and motor cortex for speech generation\textsuperscript{2,56}. Although this model
provided an useful framework for the study of language and language impairments,
modern developments in experimental techniques (positron emission tomography,
functional MRI, event-related electrical potentials) as well as newer neuropsychological
studies of language impairments, showed that more areas of the brain are involved in
language, and proved that even the roles of Broca’s and Wernicke’s areas are more
complex than was thought initially.

According to this modern approach, the processing of language requires a large
network of interacting brain areas both cortical and subcortical. Neural sensory, motor
and associative mechanisms are interconnected and essential for language production and
perception. A complex system analyzes incoming auditory signals and ensures phonemic
and grammatical construction and articulatory control. It includes: Broca’s area,
Wernicke’s area, angular gyrus, motor cortex, auditory cortex and somatosensory cortex,
supramarginal gyrus, insular cortex and the left basal ganglia complex. Other areas in the
prefrontal, temporal, parietal cortices are also involved in processing different aspects of
language\textsuperscript{2,45}.
2.2.2. Neuroimaging studies of language

Brain lesion studies as well as behavioral studies of neuropsychological impairments are insufficient for providing a complete and accurate view of language neuroanatomy. It is sometimes difficult to interpret these findings due to the complexity of cognitive deficits associated with a neuropsychological profile. It is also difficult to distinguish if a certain impairment is associated with lesioned brain area or the connection passing through that area. Moreover multiple functional deficits are often encountered in patients with large lesions and make it difficult to relate specific deficits
to specific anatomical regions. Evidence from neuroimaging studies complements the findings from brain damaged patients and makes it possible to identify a complete set of brain regions associated with a specific task\textsuperscript{56-59}. Other advantages of functional neuroimaging over lesion studies include the possibility of non-invasive, in vivo observation of neurologically normal individuals, visualization of functions in regions where lesions are rare, or observation of neuronal reorganization or brain plasticity following brain lesions. Functional neuroimaging is not limited to a certain area of the brain, so it can identify a distributed system involved in language processing, which further allows the identification of abnormal function in apparently undamaged area or normal function in/around lesioned areas.

Neuroimaging studies of auditory and visual word processing confirm the simple neurological model implicating the primary auditory, visual and motor cortices as well as Wernicke’s and Broca’s areas. Besides these, other details were detectable: bilateral activation rather than just left lateralization, specialized localization in either pars opercularis or pars triangularis, the posterior and anterior parts of Broca’s area, no activation in the angular gyrus but some activation in the fusiform gyrus. These will also guide future lesion studies to further understand the implications of involvement of these areas. Complex language tasks activate a multicomponent processing system, summarized in Table 2.1 as obtained from reviews of imaging studies\textsuperscript{56-59}. The roles of different areas of the brain in language processing were inferred from brain activation during specific tasks. This table also includes the Brodmann areas (BA) notations (Fig. 2.16) for these language regions.
Fig 2.16: Brodmann notation for areas of the brain (reproduced from http://upload.wikimedia.org/wikipedia/en/7/7b/Brodmann_areas_outline.gif).
<table>
<thead>
<tr>
<th>Language process</th>
<th>Activated area</th>
<th>BA</th>
<th>Lateralization</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Language input–auditory</td>
<td>posterior STC</td>
<td>posterior 21/22</td>
<td>bilateral</td>
<td>auditory input</td>
</tr>
<tr>
<td></td>
<td>posterior MTC (Wernicke’s area)</td>
<td>21/22</td>
<td>bilateral</td>
<td>semantic access and analysis (left) polymodal area with auditory, visual and somatosensory projections; considered site for higher language functions</td>
</tr>
<tr>
<td></td>
<td>IFG (Broca’s area)</td>
<td>44/45</td>
<td>bilateral</td>
<td>word perception and production</td>
</tr>
<tr>
<td>Language input-Silent reading</td>
<td>posterior ITC (fusiform gyrus)</td>
<td>37</td>
<td>left</td>
<td>word retrieval regardless of stimulus modality</td>
</tr>
<tr>
<td></td>
<td>posterior MTC (Wernicke’s area)</td>
<td>21/22</td>
<td>left</td>
<td>semantic access and analysis; acoustic/phonological representations necessary for silent reading</td>
</tr>
<tr>
<td></td>
<td>angular gyrus</td>
<td>39/40</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IFG (Broca’s area)</td>
<td>44/45</td>
<td></td>
<td>word perception and production</td>
</tr>
<tr>
<td></td>
<td>occipital and occipito-temporal cortices</td>
<td>18/19/37</td>
<td>bilateral</td>
<td>visual input and analysis</td>
</tr>
<tr>
<td></td>
<td>ACC</td>
<td>24/32</td>
<td>bilateral</td>
<td>written word recognition, attention</td>
</tr>
<tr>
<td></td>
<td>SMA</td>
<td></td>
<td>right</td>
<td>motor planning and imagination of articulation</td>
</tr>
</tbody>
</table>

Table 2.1: Language functions and the areas of the brain involved in their processing (summarized from Ref 56-59). ACC= anterior cingulated cortex; STC=superior temporal cortex; SMA=supplemental motor area; MTC= middle temporal cortex; ITC=inferior temporal cortex; IFG=inferior frontal gyrus.

Continued
Table 2.1 continued

<table>
<thead>
<tr>
<th>Speech production (repeat words vs read words)</th>
<th>anterior temporal lobe</th>
<th>22</th>
<th>bilateral</th>
<th>accessing meaning of words</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFG pars opercularis</td>
<td>44</td>
<td>left</td>
<td>word production</td>
<td></td>
</tr>
<tr>
<td>insula</td>
<td></td>
<td>left</td>
<td>word retrieval regardless of stimulus modality</td>
<td></td>
</tr>
<tr>
<td>posterior superior temporal sulcus</td>
<td></td>
<td>left</td>
<td>polymodal area with auditory, visual and somatosensory projections; considered site for higher language functions.</td>
<td></td>
</tr>
<tr>
<td>posterior STC</td>
<td>41/42/22</td>
<td>bilateral</td>
<td>hearing spoken responses</td>
<td></td>
</tr>
<tr>
<td>peri-sylvian sensorimotor cortices</td>
<td>3,4</td>
<td>bilateral</td>
<td>articulation using tongue, lip, larynx</td>
<td></td>
</tr>
<tr>
<td>thalamus</td>
<td></td>
<td>left</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cerebellum</td>
<td></td>
<td>medial</td>
<td>articulatory level of speech production</td>
<td></td>
</tr>
<tr>
<td>ACC</td>
<td>24/32</td>
<td>bilateral</td>
<td>initiation of speech</td>
<td></td>
</tr>
<tr>
<td>SMA</td>
<td>6</td>
<td>bilateral</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.2.2.1. Semantic priming

Semantic priming is the facilitation of the response to a target word when it follows a semantically related prime and can be explained in terms of a network model of lexicon organization\(^{60,61}\). This model assumes that activation of the prime will serve as a
source of spreading activation in the network, lowering the threshold for neighboring
nodes. Therefore, related targets (closer nodes) will be recognized faster because they are
already activated to some degree. Support for such a model is provided by lexical
decision experiments. Typically, such experiments are done as follows: a briefly
presented prime word (table) is followed by a target letter string which may be a real
word (chair) or a non-word (phonil), and participants are asked to make a decision about
the target (is it a real word or not?). The real word target may be either related or
unrelated to the prime, and priming effects are quantified by comparing the response
times (RT) to the target in different semantic relationship conditions.

Information regarding the spreading and activation of the semantic network can
be obtained by varying the semantic distance (i.e. the level of association) between the
prime and the target word, as well as by manipulating the time between the presentation
of the prime and target, also known as the stimulus onset asynchrony (SOA)\textsuperscript{61,62}.

Different levels of association between the prime and target word can yield differential
semantic priming effects. The strongest effect is observed for direct priming, when the
target word is closely related to the prime (e.g. table-chair). A weaker effect is observed
for mediated (or indirect) priming, when the prime and target are not directly associated,
but are both related to another word that establishes the link between them (e.g. lion-
stripes, mediating word is tiger). By varying the SOA, automatic versus controlled
processing can also be examined. It has been suggested that processing is automatic at a
short SOA (less than 250ms), while longer SOAs allow additional mechanisms, such as
expectancy and strategy, to be utilized, which result in more controlled processing\textsuperscript{61-63}.  

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Although behavioral studies of semantic priming have been extensively used to
determine the spread and flexibility of the semantic network, both in normal and neurologically
impaired individuals\textsuperscript{62,90-94}, for a complete understanding of this phenomenon, it is essential to
determine its neural correlates. Neuroimaging techniques, such as fMRI and PET provide the
means to explore the neural correlates of priming by allowing one to examine brain areas
that are activated during performance of tasks for which priming effects are observed.
They also permit investigation of how activation levels change when items are primed.
The most common finding in functional neuroimaging studies of priming is a decrease in
brain activation for primed versus unprimed stimuli\textsuperscript{63-67}. As for the cerebral localization
of the processes involved in semantic priming, the results reported so far are inconsistent.
During automatic processing, reduced brain activity for related versus unrelated word
pairs has been observed in the left inferior frontal gyrus (LIFG)\textsuperscript{64-66}, a region identified in
numerous neuroimaging studies as critical for retrieval, selection and evaluation of
semantic information\textsuperscript{68-72}. Neuroimaging studies have also found similar behavior in
more posterior brain structures such as the superior and middle temporal gyri\textsuperscript{63-67}. It has
been suggested that these regions play a role in semantic memory and storage of semantic
representations\textsuperscript{64,67}. In addition, bilateral activation in the middle frontal gyrus (MFG)
modulated by priming effects, has been demonstrated\textsuperscript{65,67} and is proposed to be the result
of an extensive search of the semantic network, and retrieval effort\textsuperscript{65,73}.

It has been suggested that pure automatic processing should yield priming effects
in “semantic” areas of the brain, while controlled processing should also implicate an
additional “attentional” network. Activation in the anterior cingulate cortex (ACC)\textsuperscript{63,66}
superior parietal lobe and right premotor cortex is believed to reflect the involvement of these areas in the attentional aspects of semantic priming.

Most of these studies were mainly concerned with the anatomical correlates of semantic priming, specifically looking at brain activation during related and unrelated word pair presentation. Our goal was to contribute by clarifying the inconsistencies existent in the literature regarding the brain areas involved in the semantic priming process. Also, we wanted to explore the effects on brain activation of varying semantic distances (i.e. direct and indirect priming) and of L-Dopa which, to our knowledge, have not been studied until now.

2.2.2.2. Semantic and phonological processing

Components of language processing are hierarchically organized. The main subcomponents of language processing are the phonological (auditory form of words), orthographic (visual form of words) and semantic (meaning of words) processes. The hierarchy and interaction of these systems during processing of words is presented in Fig. 2.17. Although there is a distinction between the lexical forms involved in spoken and written language, the semantic system is common for both of these. According to this model, every word, regardless of input modality is firstly processed at sublexical levels (either phonological or orthographic). After that the mental lexicon is accessed, at orthographic and phonological level, then the deeper semantic level processing follows, if necessary. If no meaning processing is required, this step is omitted so that the words can be produced/reproduced only at the low level of processing (phonological and orthographic). A vast body of literature, including both behavioral and neuroimaging
studies, concerning memory encoding and maintenance of information in memory stores also describes the semantic and phonological processes in terms of depth of processing of items. The results of these studies support the conclusion that memory performance depends on the level of processing required by the task. Stimuli that are processed at a deeper level are better encoded and longer maintained in the memory stores, while superficial encoding results in lower recall performance. Within this framework semantic processing is considered a deep process whereas phonological properties are processed at a perceptual, surface level. Perceptual, acoustic information is stored in the short term storage while the long term storage is largely semantic.

There have been numerous attempts to identify the neural correlates of the semantic and phonological language processes (also for reviews see Fiez, Price). The findings of neuroimaging studies revealed common areas activated by the two processes as well as distinguishable areas specific for each process. The left inferior prefrontal cortex constitutes a network that activates during controlled processing of both semantic and non-semantic information, whereas posterior regions are involved in retrieval of stored information such as word meaning (posterior middle temporal gyrus-BA21) or sound (parietal cortex-BA7/40). These studies go further and separate distinct regions within the prefrontal cortex involved predominantly in either semantic (anterior left inferior prefrontal cortex- BA 45/47/10) or phonological (posterior left inferior prefrontal cortex-BA 44/6) processing. McDermott et al. have also found that areas of the middle frontal gyrus (BA6, pre-SMA), bilateral fusiform gyrus (B37) and bilateral cerebellum were activated by both phonological and semantic tasks relative to baseline (fixating on a cross-hair).
Fig. 2.17: Model for single word visual and auditory processing\textsuperscript{56,59,75}.
Subcortical structures have also been found to contribute to both semantic and phonological processing. Crosson et al. showed that the left dorsal caudate and the ventral anterior thalamus contribute to retrieval of words from pre-existing lexical stores, due to direct connections with the pre-SMA. They have also suggested that right basal ganglia activity contributes by suppressing right frontal activity from interfering with language production.

Although, the areas of the brain involved in semantic and phonological processing have been clearly identified and further specifications of functional distinctions within these areas have been made, the interaction between these areas during language processing has not been extensively reported to our knowledge. Therefore, we intended to contribute to the general findings by adding information about the functional connectivity in the brain during language processes, specifically semantic and phonological processing. Also, since administration of L-dopa has been shown to result in restricted semantic networks, we wanted to explore whether this also affects the interaction between language network components, as revealed by functional connectivity.

2.3 L-Dopa and the dopaminergic and noradrenergic systems

Communication of information between neurons is accomplished by chemicals, called neurotransmitters. These are concentrated in vesicles in the presynaptic terminal. The arrival of the action potential at the synapse triggers an increase of the membrane permeability to calcium, allowing Ca entry into the presynaptic terminal, which will cause the vesicles to release their neurotransmitter contents in the synaptic cleft. The neurotransmitter molecules cross the synapse and bind to receptor sites on the post
synaptic terminal causing either the excitation or inhibition of the post synaptic neuron. Whereas some neurotransmitters trigger action potentials, others are also involved in modulating the action potentials.

A major class of neurotransmitters is the catecholamines: dopamine, norepinephrine and epinephrine. High catecholamine levels in blood are associated with stress. Catecholamines cause general physiological changes such as increases in heart rate, blood pressure, and blood glucose levels.

2.3.1. L-Dopa biochemistry

The catecholamines are all synthesized from the amino acid tyrosine in a common pathway (Fig 2.18). Tyrosine is produced in the liver and then transported to catecholamine-secreting neurons where a series of reactions convert it to dopamine, and then, if necessary to norepinephrine and finally to epinephrine.

The first step of the synthesis involves the enzyme tyrosine hydroxylase which converts tyrosine to L-dihydroxyphenylalanine (L-Dopa). Next, L-Dopa is decarboxylated to yield dopamine and CO$_2$. The enzyme dopamine $\beta$-hydroxylase then converts dopamine to norepinephrine and finally another enzyme, phenylethanolamine-N-methyl transferase transforms norepinephrine into epinephrine.

The synthesis occurs in the postganglionic neurons of the sympathetic nervous system, in the adrenal medullary cells and in certain neurons in the brain. The conversions from tyrosine to L-Dopa and then to dopamine take place in the cytoplasm of the cells in the central nervous system (CNS). The norepinephrine is synthesized within the storage vesicles in the locus ceruleus. In the neurons utilizing dopamine as a
transmitter, the dopamine β-hydroxylase enzyme is not present, thus preventing dopamine from converting to norepinephrine. The synthesis of epinephrine from norepinephrine takes place in the adrenal medulla, where the norepinephrine must be released from vesicles to be methylated to form epinephrine in the cytoplasm. Then, in order to be released as a neurotransmitter, epinephrine must be repackaged into other vesicles. Neurons that use norepinephrine as a transmitter do not express N-phenylethanolamine-methyltransferase, but neurons that release epinephrine express all the enzymes involved in the synthesis pathway\textsuperscript{2,85}.

Fig. 2.18: Synthesis of catecholamines (reproduced from Ref. 85).
2.3.2. Dopaminergic system

Dopamine has important roles in the regulation of movement, affect, cognition, thought disorder, reward and hormone release.

Most brain dopamine neurons are found within the substantia nigra (SN) and the ventral tegmental area (VTA), in the midbrain. The four major dopamine pathways in the brain are:

1. The **mesocortical pathway** which projects from the VTA to the cortex, particularly the frontal lobes. It is essential to the normal cognitive function of the dorsolateral prefrontal cortex and is thought to be involved in motivation, planning, social behavior and emotional response. This pathway is thought to be associated with the negative symptoms of schizophrenia.

2. The **mesolimbic pathway** links the VTA in the midbrain to the nucleus accumbens, ventral striatum parts of amygdala and hippocampus, lateral septal nuclei, the entorhinal cortex and the anterior cingulate cortex in the limbic system. It is thought to be involved in feelings of reward and desire. Because of this, this pathway is heavily implicated in neurobiological theories of addiction. Disruption to dopamine function (particularly, an excess of dopamine) in this area has been linked to psychosis and the positive symptoms of schizophrenia (particularly delusions and hallucinations). Also, in Parkinson's disease dopamine neurons are lost in the mesolimbic pathway although not as fast as in the nigrostriatal pathway.
3. **Nigrostriatal pathway** connects the SN with the striatum. It is particularly involved in the production of movement, as part of the basal ganglia motor loop. Loss of dopamine neurons in the substantia nigra is one of the main pathological features of Parkinson's disease, in which a person loses the ability to initiate controlled movements. This pathway is also implicated in producing tardive dyskinesia (involuntary movements mostly affecting the tongue), one of the side effects of antipsychotic drugs.

4. The fourth dopaminergic pathway, the *tuberoinfundibular tract*, runs between the hypothalamus and the pituitary gland. This pathway is involved in hormonal regulation, maternal behaviour, pregnancy and sensory processes.

### 2.3.3. **Noradrenergic system**

Norepinephrine has a role in arousal (depression and anxiety), sleep/waking cycle and vigilance. It is also one of the 'stress hormones' and affects parts of the human brain where attention and impulsivity are controlled. Along with epinephrine it affects the fight-or-flight response, activating the sympathetic nervous system to directly increase heart rate, release energy from fat, and increase muscle readiness\textsuperscript{87}.

The cell bodies of noradrenergic neurons are clustered in the locus coeruleus (LC) and the lateral tegmental nuclei (LTN) in the brainstem. The LC contains 45% of the noradrenergic neurons in the brain. The frontal cortex, hippocampus, and olfactory bulb receive noradrenergic projections exclusively from the locus coeruleus. The LTN neurons project exclusively to nuclei of the hypothalamus. Other areas such as cerebellum, spinal cord, amygdale and septum are innervated by neurons from both LC and LTN\textsuperscript{2,87}.  

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The locus coeruleus has been identified as a pleasure center, but it does also contribute to anxiety. Increased neuronal activity of the LC is seen upon the occurrence of unexpected sensory events and norepinephrine levels in the brain increase in conditions of stress. Projection of norepinephrine from the LC to the forebrain is a key feature of awareness-arousal\(^2,88\).

### 2.3.4. L-Dopa and the Language System

Behavioral research has demonstrated a role of the catecholamine neurotransmitter systems in modulation of cognition, more specifically of language networks. It has been shown that administration of L-dopa, which is converted into both dopamine and norepinephrine, regulates the access to the semantic networks and the semantic priming effect described previously in Section 2.2.2.1.

The norepinephrine and dopamine act to “amplify strong signals and dampen weak ones”\(^89\), and therefore they increase the signal-to-noise ratio of cortical information processing. This also means that increased levels of catecholamines should increase the focus of activation in semantic networks, and therefore it should decrease the spread of activation. Previous behavioral research demonstrated that administration of L-Dopa resulted in restriction of the semantic network in a lexical priming experiment\(^62,90\). This result has been correlated with studies of semantic network spread in neurologically impaired patients. Schizophrenic patients showed an increased mediated priming effect, suggesting that dopamine may play a role in modulation of semantic processing\(^91,92\). However, semantic priming in patients with Parkinson’s disease (PD) has yielded mixed results\(^94,95\). Although some studies suggest that language processing in PD is affected by
decreased signal-to-noise ratio associated with decreased levels of dopamine\textsuperscript{94}, others have not found any alterations in the processing of semantic information in PD patients\textsuperscript{95}. However, as L-Dopa is converted into both NE and DA, it is unclear whether the semantic networks are modulated by dopamine or norepinephrine. Further studies using agonists and antagonists that specifically target either noradrenergic or dopaminergic receptors are necessary in order to identify the specific roles of these systems in language processing.
3.1. Research Participants

The participants recruited for these studies were all native English speakers, right handed, as assessed with the Edinburgh Handedness Inventory\textsuperscript{95}, with no history of psychiatric or neurological problems, or of learning disabilities such as dyslexia. All participants reported normal or corrected-to-normal vision. In order to avoid the hemodynamic effects of these agents on BOLD signal, the participants were asked to abstain from caffeine and nicotine at least 2 hours prior to the study. They were also screened to comply with the MRI safety requirements (no metal implants or prostheses, no metal objects in their bodies, non-claustrophobic). Written consent was obtained from all participants in accordance with the regulations of the Institutional Review Board of The Ohio State University.
3.1.1. Semantic Priming – pilot study

Twelve participants, 6 male and 6 female, mean age 25.8 years (range 19-32 years), average school education 15 years, participated in this part of the project. No other exclusion criteria were used in addition to the ones mentioned above.

3.1.2. Pharmacological modulation studies

Sixteen participants, 8 male and 8 female, mean age 28.3 years (range 21-49 years), average school education 15 years, were recruited to participate in these studies. Additional exclusion criteria for participants in the pharmacological part of these studies were: previous or current use of drugs that stimulate or block dopamine, previous history of unprovoked hallucinations, and previous adverse reaction to drugs that stimulate dopamine.

3.2. Experimental set-up and paradigm design

3.2.1. Equipment set-up

All stimuli were presented visually using a projection system set-up in the control room. A laptop computer using SuperLab experiment generator software (Version 2.0, Cedrus Corp.), was connected to a Dell 3200MP projector to project the stimuli on a white screen. Participants were able to see the screen from the MRI scanner through a mirror mounted on the head coil. When responses from participants were required, they were able to do so by pressing the appropriate button on an fMRI-compatible response pad, part of the Lumina LP 400 system from Cedrus Corporation. A detailed description
and schematics of the experimental set-up is presented in APPENDIX C. Response times and accuracy were recorded using SuperLab.

The connection between the computer running the software and the fMRI compatible response buttons was done through the control box of the Lumina system and corresponding connecting cables. The same control box was used to acquire a trigger signal produced by the MRI system hardware, every time there was an RF pulse. This allowed the start of the presentation of the stimuli to be triggered by the first RF pulse, thus synchronizing the image acquisition with the presentation of the stimuli, which is essential for the event related studies. The trigger signal and subject responses collected by the control box, were also passed to a second laptop computer. This allowed the simultaneous recording of these two signals by using “Ezlog” software: www.sph.sc.edu/comd/rorden/ttlrecord/home.html. While the SuperLab software collects the time needed by the participant to respond to a particular stimulus, relative to the onset of that stimulus, the Ezlog software records the absolute time (i.e. time passed since the beginning of the image acquisition) of subject responses. For the event related experiments, which use brief stimuli (sometimes shorter than TR), it is very important to know the exact timing of the stimulus relative to the acquisition time. Since it appeared that any errors made by the participants in their responses, and the collection of scanner trigger introduced delays in the presentation of the stimuli with SuperLab, it was necessary to correlate the times recorded by SuperLab with the times recorded by Ezlog. This allowed the coordination of the presentation of the stimulus with the acquisition times, and it was accomplished by using a Visual Basic script (APPENDIX D), which gathered together the Excel data files recorded with both SuperLab and Ezlog, and sorted
the events according to time and type of event. When responses were missed by the recording software (e.g. when subject response was simultaneous with scanner trigger signal, Ezlog would record only scanner trigger, thus missing the subject response), manual manipulation of the files was necessary, in order to re-align the response from Ezlog with those from SuperLab. The final output of this process was a data file containing the stimuli sorted by their type, along with their onset times (relative to the beginning of image acquisition) and the subject response times and accuracy. This was used for setting up the GLM analysis of functional data, using FSL software (see Section 3.4 Data Analysis).

3.2.2. Drug administration and test order

This section refers to the pharmacological part of the project, and does not include the block design semantic priming experiment.

Due to the unavoidable inter-subject variability in brain activation detected with fMRI, the detection of drug effects benefits from a within subject (or repeated measures) design in which each participant is scanned following administration of placebo as well as following administration of one active compound (drug).

Dopamine does not cross the blood-brain barrier, therefore it is ineffective when administered peripherally. L-Dopa, which crosses the blood-brain barrier and is a precursor for dopamine, can be administered to increase dopamine levels. L-Dopa is rapidly absorbed from the small intestine, and reaches peak plasma levels in 1-2 hours after oral dose, with a half-life between one and three hours. Because only 1-3% of administered levodopa reaches the brain, to achieve therapeutic levels either a high dose
or administration along with dopa decarboxylase inhibitor, is necessary. Carbidopa is such an inhibitor typically administered with L-Dopa to minimize peripheral adverse reactions (e.g. nausea and vomiting). It does not cross the brain-blood barrier and does not prevent central conversion\textsuperscript{110}. Therefore we used for this study a combination of L-Dopa (100mg) and carbidopa (25mg).

In order to assess the drug effect on global CBF, an fMRI scan before and after drug administration was collected. Because the motor and visual activations are the most reliable and give the highest BOLD signal change in FMRI studies, a combined motor and visual task was selected for this part of the study. Participants were first scanned before any drug was administered, thus allowing us to obtain an anatomical scan and a functional scan (motor and visual tasks) before drug administration. Then a pill, either placebo or L-Dopa/carbidopa, was orally administered and the participant waited for one hour before the next group of scans. Subsequently, the group of scans listed in Table 3.1 was performed. The pre- and post- drug/placebo administration MRI scans and tasks during one session is summarized in Table 3.1.

The order of drug administration was counterbalanced (some participants were administered placebo during their first session and L-Dopa during their second session, while others were administered the L-Dopa first and placebo second). To avoid confounds such as practice and task difficulty, the order of the language tests was also counterbalanced, as presented later in this chapter. The test sessions for each participant were separated by at least a week.

Heart rate and blood pressure were measured before administration of the drug, and then immediately before and after the MRI scans.
Practice trials were performed for all experiments inside the scanner, prior to data acquisition, until participants were comfortable with the task and the scanner conditions.

The practice language tasks stimuli were not reused throughout the duration of the experiment.

<table>
<thead>
<tr>
<th>MRI scans and timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-drug scans:</td>
</tr>
<tr>
<td>1. localizer</td>
</tr>
<tr>
<td>2. anatomical</td>
</tr>
<tr>
<td>3. motor+visual (block design)</td>
</tr>
<tr>
<td>Drug administration and waiting time</td>
</tr>
<tr>
<td>1 hour</td>
</tr>
<tr>
<td>Post-drug scans</td>
</tr>
<tr>
<td>1. localizer</td>
</tr>
<tr>
<td>2. anatomical</td>
</tr>
<tr>
<td>3. semantic priming (ER design)</td>
</tr>
<tr>
<td>4. motor+visual (block design)</td>
</tr>
<tr>
<td>5. semantic priming (ER design)</td>
</tr>
<tr>
<td>6. functional connectivity (block design)</td>
</tr>
<tr>
<td>7. functional connectivity (block design)</td>
</tr>
<tr>
<td>Total session time</td>
</tr>
<tr>
<td>2.5 - 3 hours</td>
</tr>
</tbody>
</table>

Table 3.1: MRI and drug administration protocol during a test session.
3.2.3. Paradigm design for CBF modeling experiment

Motor and visual cortices have been found to yield the largest and easiest to identify activation during fMRI experiments. Therefore a combined motor and visual task was used in order to determine the effect of the drug on cerebral blood flow and BOLD response.

In a block design experiment, 4 blocks of task (21 sec) were alternated with 5 blocks of rest (33 sec) for a total of 4 min 21 sec. During the task blocks, participants watched a black and white flickering checkerboard (8 Hz) presented on the screen and were asked to push alternating buttons on the Lumina LP 400 response pad, using their right hand, the entire time they saw the flickering checkerboard on the screen. During the rest block they were asked to look at a plus sign in the middle of a black screen and relax.

3.2.4. Paradigm design for the semantic priming experiment

This was a lexical decision experiment as described in section 2.2.2.1. Word pairs were presented on the screen, one word at a time, with a high contrast (yellow words on dark blue background). The majority of the words were nouns but also included verbs, adjectives, and adverbs. All of the prime words were real English words. The target words included real words and pronounceable non-word (NW) letter strings. The prime-target pairs were categorized according to semantic relationship as defined by Kischka et al.\textsuperscript{62}: for some of word pairs the target was closely (C) related to the prime (one associative step apart: e.g. farmer – field), for other pairs the target was distantly (D) related to the prime (two associative steps apart: e.g. summer – snow) or the target was unrelated (U) to the prime (e.g. water – computer). All words and non-words consisted of
between three and seven letters. During the presentation of the targets, participants were instructed to indicate whether each was a real word or not (yes for C, D, and U pairs; no for NW pairs) as quickly as possible, by pressing the appropriate button on the previously described fMRI-compatible response system. Response times and accuracy were recorded using SuperLab software.

The semantic priming experiments were performed in two separate studies: a pilot study, which employed a block design and did not include drug administration, and a second study, part of the pharmacological modulation of language project, examining the L-Dopa effect on this process and a more complex event related paradigm design. These studies will be described separately in the following sections.

3.2.4.1. Block design

A total of 140 prime-target word pairs were presented (see APPENDIX E for a list of the word pairs used in this experiment). The target words included 100 real words (25 closely (C) related to the prime, 25 distantly (D) related to the prime and 50 unrelated (U) to the prime) and 40 pronounceable non-word (NW) letter strings. The median word length was 5 letters for both the prime and target words, and the median Kucera-Francis written word frequency $^{96}$ was 44 per million for the prime words and 26 per million for the target words, with these characteristics matched between the two runs and types of stimuli.

For this experiment, each participant performed two scanning runs of a lexical decision paradigm. One of the runs consisted of alternating blocks of closely and
unrelated word pairs, and the other run consisted of distantly and unrelated word pair blocks, as shown in Fig. 3.1.

Each task block (21s) consisted of seven word pairs, and was designed as follows:

- a C block consisted of 5 closely related word pairs and two randomly placed non-word pairs
- a D block consisted of 5 distantly related word pairs and two randomly placed non-word pairs
- an U block consisted of 5 unrelated word pairs and two randomly placed non-word pairs.

In order to avoid order effects, task epochs were counterbalanced both within runs and between runs (i.e. for some participants the runs would start with a C/D block and end with an U block, for others it would start with an U block and end with a C/D block; also, some participants would see a CU run first and DU run second, while other will see a DU run first and a CU second). This is presented in Table 3.2.

Each word pair was designed as follows: the prime word was presented for 400ms followed by a plus sign (+) for 300ms, and then the target word (either a real word or a non-word) for 1.3s. A blank screen (1s) separated each of the word pairs. This design is exemplified for a closely related word pair in Fig. 3.2.
Fig. 3.1: Design of semantic priming block design with 10 task blocks lasting 21s alternating with 11 rest blocks (fixation point in the middle of the screen) 15s long.
Table 3.2: The type of runs and the order of tasks within runs performed by each participant.

<table>
<thead>
<tr>
<th>Participant</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run1</td>
<td>CU</td>
<td>UC</td>
<td>DU</td>
<td>UD</td>
<td>CU</td>
<td>UC</td>
<td>DU</td>
<td>UD</td>
<td>CU</td>
<td>UC</td>
<td>DU</td>
<td>UD</td>
</tr>
<tr>
<td>Run2</td>
<td>DU</td>
<td>UD</td>
<td>CU</td>
<td>UC</td>
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<td>UC</td>
<td>DU</td>
<td>UD</td>
<td>CU</td>
<td>UC</td>
</tr>
</tbody>
</table>

Fig. 3.2: Word pair presentation (in this case a closely related pair).
3.2.4.2. Event related design

The semantic priming paradigm is a cognitive task for which a reaction to an unexpected stimulus is probed. Therefore a better set up for this experiment is a completely randomized presentation of the stimuli, in an event related design. This will allow avoiding the anticipation and strategy effects that the block design presentation could introduce.

A total of 150 prime-target pairs were presented during each run, and four versions of such a run were used, in order to present different word pairs during each experimental condition (see APPENDIX E for a list of the word pairs used in this experiment). In each run there were 90 real word pairs (30 closely (C) related, 30 distantly (D) related and 30 unrelated (U) to the prime) and 60 pronounceable non-word (NW) letter strings. These pairs were presented in a jittered fast event related design (Fig. 2.14), in which both the types of stimuli and the inter-trial intervals (ITI= a cross-hair in the middle of the screen; there were 50 such events, 3s each) were randomized according to a schedule obtained with OPTSEQ (http://surfer.nmr.mgh.harvard.edu/optseq/).

The median word length was 5 letters for both the prime and target words, and the median Kucera-Francis written word frequency was 37 per million for the prime words and 34 per million for the target words, with these characteristics matched between types of stimuli.

For this experiment, each participant performed two runs of a lexical decision paradigm during each visit (drug or placebo). One run examined the automatic processing by employing a short stimulus onset asynchrony (SOA) of 200ms, and the other examined the controlled processing, using a long SOA of 700ms, as described in previous
The design of each word pair for either long or short SOA is presented in Fig. 3.3.

The start of the experiment was triggered by the first RF pulse, through the Lumina system. The “dummy” scans, added at the beginning of the scan to allow the magnetization to reach equilibrium, allowed us to start the presentation of the stimuli with a rest (ITI) period of 12sec, followed by the onset of the randomized event related schedule. At the end of the scan there were 18 s of rest (ITI) events to allow the BOLD signal to decay to baseline. Each run lasted either 14 min and 45 s (for the short SOA set-up) or 16 min (for the long SOA experiment).

In order to avoid practice effect 4 lists of word pairs were used (L1, L2, L3, and L4), two lists being used during one session (treatment condition), one each for the short and long SOA experiments. Two variations of each list were created: one for the short SOA paradigm (short SOA L_i) and one for the long SOA paradigm (long SOA L_i). The order in which the lists were used was counterbalanced, so that each list was presented equal times during each experimental condition: (type of drug and SOA). Each participant was presented with versions of the list counterbalanced between drug conditions, as presented in Table 3.3, and no list was repeated for the same participant.
Fig. 3.3 Design of word pairs: a) short SOA; b) long SOA. The ITI of 3s was added with each pair, so that there was at least a 3s interval between presentation of two sets of additional pairs, to avoid non-linearity effects.
Table 3.3: Version of semantic priming word lists presented to each participant during the four experimental conditions.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Visit 1- Placebo</th>
<th>Visit2- L-Dopa</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>short SOA L1</td>
<td>short SOA L3</td>
</tr>
<tr>
<td></td>
<td>long SOA L2</td>
<td>long SOA L4</td>
</tr>
<tr>
<td>S2</td>
<td>short SOA L2</td>
<td>short SOA L4</td>
</tr>
<tr>
<td></td>
<td>long SOA L3</td>
<td>long SOA L1</td>
</tr>
<tr>
<td>S3</td>
<td>short SOA L3</td>
<td>short SOA L1</td>
</tr>
<tr>
<td></td>
<td>long SOA L4</td>
<td>long SOA L2</td>
</tr>
<tr>
<td>S4</td>
<td>short SOA L4</td>
<td>short SOA L2</td>
</tr>
<tr>
<td></td>
<td>long SOA L1</td>
<td>long SOA L3</td>
</tr>
<tr>
<td>S5</td>
<td>long SOA L1</td>
<td>short SOA L2</td>
</tr>
<tr>
<td></td>
<td>short SOA L3</td>
<td>long SOA L4</td>
</tr>
<tr>
<td>S6</td>
<td>long SOA L2</td>
<td>short SOA L3</td>
</tr>
<tr>
<td></td>
<td>long SOA L4</td>
<td>short SOA L1</td>
</tr>
<tr>
<td>S7</td>
<td>long SOA L3</td>
<td>short SOA L4</td>
</tr>
<tr>
<td></td>
<td>long SOA L1</td>
<td>short SOA L2</td>
</tr>
<tr>
<td>S8</td>
<td>long SOA L4</td>
<td>short SOA L1</td>
</tr>
<tr>
<td></td>
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<td>short SOA L3</td>
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<tr>
<td>S9</td>
<td>short SOA L1</td>
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</tr>
<tr>
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<td>long SOA L4</td>
</tr>
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<td>S10</td>
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<td>short SOA L4</td>
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<tr>
<td></td>
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<td>long SOA L1</td>
</tr>
<tr>
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</tr>
<tr>
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<td>long SOA L4</td>
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</tr>
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<td>S12</td>
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<td>short SOA L2</td>
</tr>
<tr>
<td></td>
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<td>long SOA L3</td>
</tr>
<tr>
<td>S13</td>
<td>long SOA L1</td>
<td>short SOA L2</td>
</tr>
<tr>
<td></td>
<td>short SOA L3</td>
<td>long SOA L4</td>
</tr>
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<tr>
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<td>short SOA L2</td>
</tr>
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</tr>
<tr>
<td></td>
<td>long SOA L2</td>
<td>short SOA L3</td>
</tr>
</tbody>
</table>
3.2.5. Paradigm design for functional connectivity experiment

This experiment was designed to study the semantic and phonological processes, by asking the participants to attend to the meaning and sound of words presented on the screen, one word at a time, with a high contrast (yellow words on dark blue background).

Four word lists (see APPENDIX F for the word lists used in this experiment), two for the semantic processing (sem1 and sem2 in Table 3.4) and two for the phonological processing (phono1 and phono2 in Table 3.4), were used as stimuli in this experiment. These were selected and modified from the sets used by McDermott et al\textsuperscript{80}, which have demonstrated activation patterns on fMRI that dissociate the semantic and phonological language processes. The median word length was 5 letters for both semantic and phonological lists, and the median Kucera-Francis written word frequency\textsuperscript{96} was 32 per million for the semantic lists and 30 per million for the phonological lists, with these characteristics matched between the four different lists. The four lists were counterbalanced within and between sessions as presented in Table 3.4 (i.e. some of the participants were presented with the semantic task first and phonological second, others were presented with the phonological first and semantic second; each version of the lists was presented equal times in each experimental condition, and no version was repeated for the same participant).
<table>
<thead>
<tr>
<th>Participant</th>
<th>Visit 1- Placebo</th>
<th>Visit2- L-Dopa</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>phono1</td>
<td>phono2</td>
</tr>
<tr>
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<tr>
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<td>phono2</td>
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</tr>
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</tr>
<tr>
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</tr>
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<td>sem2</td>
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<td>sem1</td>
</tr>
<tr>
<td></td>
<td>phono2</td>
<td>phono1</td>
</tr>
<tr>
<td>Participant</td>
<td>Visit 1- L-Dopa</td>
<td>Visit2- Placebo</td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>S9</td>
<td>phono1</td>
<td>phono2</td>
</tr>
<tr>
<td></td>
<td>sem1</td>
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<tr>
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<td>sem1</td>
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</tr>
<tr>
<td></td>
<td>phono2</td>
<td>phono1</td>
</tr>
</tbody>
</table>

Table 3.4: Version of semantic and phonological word lists presented to each participant during the four experimental conditions.
For this experiment, during each test session (one session per drug condition), each participant performed two scanning runs. One of the runs consisted of alternating blocks of semantic task (24 sec) and rest (30 sec), and the other run consisted of alternating blocks of phonological task (24 sec) and rest (30 sec), for a total of 4 min and 6 sec for each run, as shown in Fig. 3.4 and 3.5.

Each task block (24 sec) consisted of 15 words: for the semantic condition 10 of the words in the list were related by meaning and 5 were unrelated to a cue word, while for the phonological condition 10 of the words rhymed and 5 did not rhyme with the cue word. The design of a block was as follows: a cue word was presented in capital letters for 3 seconds followed by the list of 15 words. Each word in the list was presented for approximately 1100 ms, with a 300 ms inter-stimulus interval (a blank screen), for a total of for 1.4 seconds for each word, as presented in Fig 3.4 and 3.5.

Participants were instructed to attend to the meaning or sound of the lists presented. They responded by pressing one of the two buttons on the fMRI-compatible response system as follows: for the semantic processing run, they were asked to respond with YES (left button) if the word in the list was related by meaning to the cue, and with NO (right button) if the word was not related to the cue; for the phonological task, participants were asked to respond with YES if the word rhymed with the cue and with NO if the word did not rhyme with the cue. Response times and accuracy were recorded using SuperLab.
Fig 3.4: Design of a semantic run and an example of a semantic task block.
Fig 3.5: Design of a phonological run and an example of a semantic task block.
3.3. Imaging data acquisition

3.3.1. Semantic Priming – pilot study

Images were collected with a 1.5 T General Electric (Milwaukee, WI) Signa scanner equipped with a quadrature head coil. Structural T1-weighted images were acquired for anatomic localization and co-registration, using the 3D FAST SPGR pulse sequence (256x128 matrix; 240mm FOV; 60 axial slices; 2.5mm slice thickness). GE’s prototype EPIBOLD/EPIRECON tools were used to collect and reconstruct off-line the BOLD contrast functional data (gradient echo EPI sequence; TR=3s; TE=40ms; $\alpha=90$; FOV=240mm; matrix 64x64, 28 axial slices, 5mm thick). Total time for the functional scans was 6min 24s. The first three image volumes were acquired to allow stabilization of longitudinal magnetization, and were discarded before data analysis.

3.3.2. Pharmacological modulation studies

Images were collected with a 1.5 T General Electric (Milwaukee, WI) Signa scanner with a quadrature head coil. The scanner was also equipped with an fMRI acquisition software, BrainWaveRT (General Electric), which allows for preparation, acquisition and visualization of functional images. Structural T1-weighted images were acquired for anatomic localization and co-registration, using the 3D FAST SPGR pulse sequence (256x128 matrix; 240mm FOV; 64 axial slices; 2.5mm slice thickness). The BOLD contrast functional data were collected using a gradient echo EPI pulse sequence (TR=3s; TE=40ms; $\alpha=90$; FOV=240mm; matrix 64x64, 28 axial slices for whole brain coverage; 5mm slice thickness). The first four image volumes were acquired to allow stabilization of longitudinal magnetization, and were discarded before data analysis.
3.4. Data analysis

3.4.1. Imaging Data Analysis - Individual and group activation maps

The imaging data were analyzed using FSL\textsuperscript{97}, and AFNI\textsuperscript{98} software. Pre-statistics processing was performed using FSL and consisted of motion correction\textsuperscript{99}, non-brain signal removal\textsuperscript{100}, Gaussian spatial smoothing (FWHM 5mm), intensity normalization of all volumes by the same factor, and high-pass temporal filtering.

In order to identify the areas of the brain activated by different tasks, individual and group analyses were performed with FSL. Statistical analysis was carried out by first using FILM (FMRIB’s Improved Linear Model) to create individual activation maps, and then FLAME (FMRIB’s Local Analysis of Mixed Effects)\textsuperscript{101} was used to generate average group maps. Z statistic images were obtained using cluster analysis with clusters determined by $Z>3$ and a cluster significance threshold of $p=0.05$\textsuperscript{102}-\textsuperscript{104}. Registration to the MNI standard brain (Montreal Neurological Institute-MNI defined a standard brain by using an average of a large series of MRI scans on normal controls) was also carried out\textsuperscript{99,105}.

3.4.2 Data analysis for CBF modeling experiment

Individual activation maps were obtained for each of the four scans for each participant (Scan1=Placebo visit: pre-drug, Scan2=Placebo visit: post-drug, Scan3=L-Dopa visit: pre-drug, Scan4=L-Dopa visit: post-drug) for a total of 64 data sets. Due to excessive motion during the scans, 5 sets of data were discarded, resulting in the following distribution: Scan1: $n=15$; Scan2: $n=15$; Scan3: $n=16$; Scan4: $n=13$. 

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The individual activation maps were then transformed to the common standard space MNI and overlaid to obtain one map of activation for each participant, showing the areas of the brain commonly activated in all four scans. In order to obtain ROIs specific to the motor and visual areas, these individual participant average maps were then masked with two standard space masks$^{106,107}$ for the left motor cortex and visual cortex respectively, obtained from a database available online at http://hendrix.imm.dtu.dk/services/jerne/ninf/voi.html. Thus two masks (left motor cortex and visual cortex) were obtained for each participant. In order to extract average BOLD signal change for each of these ROIs for each participant, the FEATQUERY program (part of FSL) was then used. This data was then further analyzed with the statistical software package SPSS, to detect significant changes in BOLD signal due to drug interaction. The BOLD signal changes after drug administration (from Scan 2 and Scan 4), were subsequently used to determine the change in baseline CBF due to drug administration, by employing the method described in Section 2.1.4, specifically equation 2.17.

3.4.3. Data analysis for the semantic priming experiment

3.4.3.1. Block design study

Different regions of interest were identified from the group activation maps and further analysis was performed in order to better characterize the difference in activation between unrelated and related word pairs. Specifically, as a more sensitive measure, individual MR signal time courses were examined. The pre-processed data sets (as described in Section 3.4.1) were analyzed via cross-correlation with a boxcar function using AFNI$^{98}$. The voxels with the highest correlation coefficients (>0.3) in the different
activated regions of the brain, either previously determined from the group maps or as reported in the literature, were identified. The MR signal time courses for these voxels were extracted. The percent signal changes associated with the three different tasks (C, D, and U), normalized to the baseline rest condition, for each region of interest and for each participant, were examined via an analysis of variance (ANOVA), and post-hoc Bonferroni comparisons were conducted in order to detect the priming effects.

3.4.3.2. Event related study

Response times and scanner trigger TTL pulses recorded with SuperLab and Ezlog during scanning sessions were sorted for each participant using an Excel Visual Basic code (see APPENDIX D), to accurately identify the onset time of each event. Then a 3 column text file, indicating the onset time, duration and value of the event (see on-line documentation for FSL General Linear Model set-up), was created and used as a model in a GLM first level analysis, thus allowing us to obtain activation maps for each participant during each scan. There were four scans per participant for a total of 64 scans: short SOA version during placebo treatment (Pla_shortSOA), long SOA version during placebo treatment (Pla_longSOA), short SOA version during L-Dopa treatment (DA_shortSOA), and long SOA version during L-Dopa treatment (DA_longSOA). Due to excessive motion during the scans or high percentage of errors in subject responses, 10 sets of data were discarded, resulting in the following distribution: Pla_shortSOA: n=14; Pla_longSOA: n=15; DA_shortSOA: n=12; DA_longSOA: n=13.

In a higher level analysis (analysis across sessions or across subjects), average group maps were obtained for each of the four conditions, for each type of stimulus (C,
D, U, NW) and direct comparisons (t-test) were performed to determine differences in
activation patterns due to: type of stimulus, SOA and drug condition.

3.4.3.3. Behavioral data analysis

For both the block design experiment and the event related experiment behavioral
data was analyzed similarly. Differences will be emphasized when appropriate.

Mean response times (RT) and error rates were calculated for each participant and
across subjects for each of the three semantic conditions. All response errors were
removed and response times (RT) below 200ms and above 1000ms were considered
outliers and excluded from analysis. This resulted in the exclusion of less than 3% of the
data. Non-word pairs were included in the design only to avoid a response bias and
therefore no further analysis was conducted for these pairs. In order to test for general
effects of semantic priming on response times, a one way ANOVA was performed with
RT as the dependent variable to determine the effect of stimulus type (C, D, U) and the
semantic priming effects. For the event related experiment, effects of type of word pair
(C, D, U), SOA (long, short) and drug (placebo, L-Dopa) were examined in a repeated
measures 3*2*2 (stimulus* SOA* drug) ANOVA.

3.4.4. Data analysis for the functional connectivity study

Individual activation maps were obtained as described before for each of the four
scans: semantic processing during placebo treatment (Pla_sem), phonological processing
during placebo treatment (Pla_phono), semantic processing during L-Dopa treatment
(DA_sem), and phonological processing during L-Dopa treatment (DA_phono) for each
participant. Due to excessive motion during the scans, 4 sets of data were discarded, resulting in the following distribution: Pla_sem: n=15; Pla_phono: n=15, DA_sem: n=15, DA_phono: n=15. For the remaining data sets, average group maps were obtained for each of the four scans performed by participants and direct comparisons (t-test) were performed to determine differences in activation patterns during semantic versus phonological processing as well as to identify any effects the drug may have on these.

3.4.4.1. ROI design and average signal time series analysis

Functional connectivity was computed for each participant, for each task and drug condition. A number of regions of interest (ROI) activated by the two tasks, were determined *a priori* for each participant, based on the findings of McDermott et al.\(^{80}\), and included the left inferior frontal cortex (BA 44/45/46)- LIFG, left fusiform gyrus (BA37)-LFUS, left parietal cortex (BA7)-LPAR and left middle temporal cortex (BA 21/22)-LMTG. Spherical ROIs (radius 10mm) with the center in the above mentioned anatomical regions were drawn on each participant’s high resolution images. These were registered to the EPI images using the registration matrices created for the registration to the MNI standard brain.\(^{99,105}\) The registration of each ROI mask was checked for each participant, in each task and drug condition, so that it contained mostly activated voxels (as determined in the first level analysis). When the overlap was not optimal, the ROI masks were re-drawn and re-registered, repeating the above procedure, until the optimal overlap was achieved. Average time series for all voxels included in the ROI were then extracted for each subject using FEATQUERY, part of FSL.
3.4.4.2. Functional connectivity calculations

Correlations of these time series between pairs of ROIs were computed as described in Section 2.1.6, specifically equation (2.19). Since the correlation coefficients thus obtained are not normally distributed, standard statistical tests cannot be performed on them. The solution is to use Fisher’s Z-transformation that converts these correlation coefficients (cc) to the normally distributed variable z (z = 0.5[ln(1+cc) - ln(1-cc)]). This transformation was applied to the set of correlations of time series, allowing us to further analyze them in a 2*2*6 (drug*task*ROI pairs) repeated measures ANOVA. This compares task, drug condition and ROI pair, within subject to determine whether the drug, task or the ROI have an effect on functional connectivity. Furthermore, for each ROI pair, functional connectivity was compared separately, using a 2*2 ANOVA for L-Dopa vs. placebo and semantic vs. phonological task.

3.4.4.3. Behavioral data analysis

Mean response times (RT) and error rates were calculated for each participant for each of the four scans. All response errors were removed and response times (RT) below 200ms were considered outliers and excluded from analysis. This resulted in the exclusion of less than 3% of the data. A repeated measures 2*2 (task*drug) ANOVA was carried out to detect the effect of either the drug or the task on response times.
CHAPTER 4

RESULTS AND DISCUSSION

4.1. The effect of L-Dopa on cerebral blood flow

4.1.1. Results

Due to excessive motion during the scans, 5 of the 64 data sets (16 subjects, 4 scans per subject) were discarded, resulting in the following distribution: Scan1: n=15; Scan2: n=15; Scan3: n=16; Scan4: n=13 (Scan1=Placebo visit pre-drug, Scan2=Placebo visit post-drug, Scan3=L-Dopa visit pre-drug, Scan4=L-Dopa visit post-drug). For the remaining data sets, group activation maps were obtained as described in Chapter 3, Section 3.4.1 for the pre-drug administration scans and post L-Dopa and post-Placebo scans. These show activation in the left motor cortex, SMA and sensory cortex (participants used their right hand to perform the motor task), as well as visual cortex, and are presented in Fig. 4.1.
Fig 4.1: Group activation maps (Z>3.5, p>0.05) for the pre-drug scans (a), post-placebo (b) and post L-Dopa (c) administration.

Direct comparison maps, using paired sample t-tests, were obtained between all runs, and no significant differences were found in the activation maps between pre and post drug administration for either drug, nor between post L-Dopa and post Placebo administration.

As described in Section 3.4.2., eight different ROIs (four for the motor cortex and four for the visual cortex) were defined for each participant or each of the experimental conditions (Scan1-4 defined above). To make sure the number of voxels included in these
ROI’s is similar between experimental conditions, they were analyzed using t-tests. The results show that the differences were not significant, i.e. the average number of voxels included in the drawn ROIs for each of the four scans was similar between these scans. This is presented in Table 4.1.

<table>
<thead>
<tr>
<th></th>
<th>Total number of voxels (averaged over all participants) in the ROI (SD)</th>
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<th>Visual cortex</th>
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</thead>
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<td></td>
<td></td>
<td></td>
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<td>1501 (166)</td>
<td></td>
</tr>
<tr>
<td>post L-Dopa</td>
<td>847 (83)</td>
<td>1503 (155)</td>
<td></td>
</tr>
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<table>
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</tr>
<tr>
<td>post L-Dopa vs post Placebo</td>
<td>0.43</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Table 4.1: Average number of voxels included in the motor and visual cortex ROIs, from which BOLD signal changes were extracted.

Direct comparisons performed on the BOLD signal changes extracted in the ROI analysis (time series were averaged for all voxels included in the ROI, see Table 4.1) described in Section 3.4.2, revealed no significant differences between the drug and
placebo conditions. Baseline (during non-active state) CBF changes induced by L-Dopa, obtained from the measured BOLD signal according to equation 2.17, were less than 1% in both visual and motor cortices. These are presented in Table 4.2.

<table>
<thead>
<tr>
<th>BOLD$^D$/BOLD$^P$</th>
<th>Motor cortex</th>
<th>Visual cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\chi = \frac{CBF_r^D - CBF_r^P}{CBF_r^P}$</td>
<td>0.70%</td>
<td>0.66%</td>
</tr>
</tbody>
</table>

Table 4.2: BOLD signal and baseline CBF changes induced by L-Dopa (D) compared to Placebo (P) administration.

4.1.2. Discussion

Pharmacological fMRI can provide information about mechanisms of the drug action in the brain as well as how these drugs affect certain brain functions.

Because the fMRI signal is not a direct measure of neuronal activity, but an indirect one, reflecting a complex combination of CBF, CBV and CMRO$_2$ changes associated with increased neural activity, it is important in pharmacological fMRI to assess the possible effect of the drug on global brain hemodynamics. If a drug has an
effect on the hemodynamic response, this effect must be either included or removed from
the interpretation of specific drug effects on areas of activation. There have been
numerous studies showing either vasoconstrictive or vasodilating effects of drugs on
cerebral vasculature, thus influencing the BOLD signal in fMRI studies\textsuperscript{11-20}. Therefore,
determination of baseline changes in blood flow and volume is important before
performing more complex tasks.

There are different means of measuring the effect of drug on cerebral
hemodynamic response, such as determination of BOLD changes during rest/baseline
condition, with and without drug, incorporation of a control task, the use of specialized
imaging pulse sequences to determine general blood flow (arterial spin labeling
sequences)\textsuperscript{21} and blood volume (use of contrast agents) changes due to drug or theoretical
modeling and simulations\textsuperscript{13} based on measured signal and known relationships between
all the hemodynamic parameters\textsuperscript{6,9}.

The aim of this part of the project was to assess any effects of L-Dopa
administration on global cerebral blood flow, specifically on baseline CBF. To our
knowledge this has not been done before. Because we did not have the means to perform
direct measurements of CBF (e.g. arterial spin labeling), we resorted to using a
theoretical model, which allowed us to calculate changes in global baseline CBF for the
measured BOLD responses as previously attempted by other research\textsuperscript{13}, in the motor and
visual cortices. More specifically the assumptions used were that that global perturbations
in CBF would affect the BOLD signal of interest and changes in basal CBF would result
in changes in baseline signal, and not in active state signal\textsuperscript{13,28,30}. The motor and visual
cortices were chosen for their well know high BOLD signal (up to 5% signal change)
during fMRI studies. Also, these areas are clearly identified and anatomically and functionally.

Motor and visual stimulation produced a significant BOLD response in all subjects, in all conditions, in the left motor cortex (right hand was used for motor task) and bilaterally in the visual cortex. Direct comparisons between activation maps in drug and placebo conditions revealed no significant differences. The absence of significant activation in the direct comparison suggests that the drug had no effect on the activation of motor and visual cortices. Moreover, when ROI analysis was performed, and average BOLD signal was extracted for each scan, no differences were found in the signal between drug and placebo condition, for either the motor or visual cortex. Furthermore, this was also reflected in the calculated changes in baseline CBF, which were less than 1% for both motor and visual cortices.

These results suggest that the administration of L-Dopa had no effect on global brain hemodynamics and no further steps need to be taken to account for such effects when specific cognitive functions (e.g. language) are studied. Therefore, in the remaining of the studies we assumed that any drug effect we would observe would reflect the modulatory effect of L-Dopa on the specific cognitive function, specifically language.

However due to the limitations of the method used to assess the changes in baseline CBF, further work needs to be done to confirm these findings. The assumptions made during the calculation of equation (2.17) were that if there was any drug effect, this would result in an increase in the baseline CBF, and that the hemodynamic parameters corresponding to the active state would not be affected. These assumptions have not been clearly confirmed experimentally by using direct measurements of CBF. It is also
uncertain if other parameters such as CBV and CMRO₂ are affected by L-Dopa. In order to indisputably determine if such effects are real, direct measurements of CBF and CBV have to be performed to determine what effect, if any, L-Dopa has on brain hemodynamics.

4.2. Functional MRI of semantic priming

4.2.1. Block design

4.2.1.1. Behavioral results

In order to test for general effects of semantic priming on response times (RT), an ANOVA was performed with RT as the dependent variable. This analysis revealed a significant main effect for type (C, D, U) of semantic relationship (F (2, 1158) =26.735, p<0.0005). Post-hoc analyses using Bonferroni comparisons revealed significantly faster response times for the closely related compared to unrelated targets, for distantly related compared to unrelated targets, and for closely compared to distantly related ones. These results are presented in Table 4.3 and Table 4.4.

4.2.1.2. Imaging results

Group activation maps obtained using FSL’s cluster analysis for each of the three semantic conditions (C, D, U) compared to rest baseline condition revealed brain activation in the left inferior frontal gyrus-LIFG (BA44/45), bilaterally in the middle frontal gyrus-MFG (BA46/9), insula, parietal cortex (BA7), and the anterior cingulate cortex-ACC (BA32/24). Visual, somatosensory, motor and premotor cortices were also
activated due to visual presentation of stimuli and required motor response. The pattern of brain activation associated with the processing of closely related, distantly related and unrelated word pairs is shown in Fig 4.2 and Fig 4.3. The MNI coordinates for the peak activity (maximum Z-score) in the regions showing a semantic priming effect are presented in Table 4.5.

<table>
<thead>
<tr>
<th>Semantic relationship between prime and target</th>
<th>RT (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C (closely related)</td>
<td>517 (61)</td>
</tr>
<tr>
<td>D (distantly related)</td>
<td>560 (66)</td>
</tr>
<tr>
<td>U (unrelated)</td>
<td>586 (71)</td>
</tr>
</tbody>
</table>

Table 4.3: Mean response times (RT) in msec (standard deviations in brackets).

<table>
<thead>
<tr>
<th>Semantic relationship</th>
<th>Mean Difference in RT in msec (SD)</th>
<th>p&lt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>unrelated vs. closely related</td>
<td>46.80 (7.8)</td>
<td>0.00005</td>
</tr>
<tr>
<td>unrelated vs. distantly related</td>
<td>24.98 (6.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>distantly related vs. closely related</td>
<td>21.81 (7.8)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 4.4: Mean priming effects as revealed by Bonferroni multiple comparisons (standard deviations in brackets).
Fig 4.2: Group activation during CU/UC runs: A-brain activation during U task compared to resting baseline; B-brain activation during C task compared to resting baseline.
Fig 4.3: Group activation during DU/UD runs: A-brain activation during U task compared to resting baseline; B-brain activation during D task compared to resting baseline.
<table>
<thead>
<tr>
<th>Location</th>
<th>CU/UC runs</th>
<th>DU/UD runs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z score</td>
<td>x</td>
</tr>
<tr>
<td>LIFG (BA 44/45)</td>
<td>U 3.86</td>
<td>-46</td>
</tr>
<tr>
<td></td>
<td>C 3.82</td>
<td>-44</td>
</tr>
<tr>
<td>Left MFG (BA 46/9)</td>
<td>U 4.63</td>
<td>-48</td>
</tr>
<tr>
<td></td>
<td>C 4.78</td>
<td>-48</td>
</tr>
<tr>
<td>Right MFG (BA 46/9)</td>
<td>U 4.83</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>C 4.43</td>
<td>46</td>
</tr>
</tbody>
</table>

Table 4.5: Maximum Z-scores for the activated brain regions showing the semantic priming effect during the two functional runs. The coordinates are given in mm for the MNI standard brain.

**MR signal time courses**

The ANOVA analysis of MR signal time course for the individual voxels with the highest correlation coefficients in the above mentioned regions of the brain revealed a difference in activation during processing of the different word pairs (C, D, and U) in the LIFG and bilateral MFG. In addition, when individual MR signal time course analysis was carried out for other areas of the brain previously reported in literature as activated by semantic priming paradigms, differential activation in the anterior temporal lobes- ATL (BA 38) in both hemispheres was also detected.
Post-hoc analyses were performed using Bonferroni comparisons and significant differences in the percent signal changes for direct and indirect priming were found. A decrease in BOLD signal change was observed when closely related word pairs were processed as compared to unrelated word pairs in the LIFG and bilaterally in the MFG and ATL. With the exception of the left ATL, an effect of the intermediate semantic relation (distantly vs. closely related) was also observed in these areas. In the left anterior ATL, the BOLD signal change for the unrelated word pairs was significantly larger than the signal during distantly related word pair processing (see Table 4.6).
<table>
<thead>
<tr>
<th>Brain area</th>
<th>Task comparison</th>
<th>Mean Difference (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIFG (BA 44/45)</td>
<td>U vs. C</td>
<td>0.29 (0.07)</td>
<td>0.00005</td>
</tr>
<tr>
<td></td>
<td>D vs. C</td>
<td>0.30 (0.08)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>U vs. D</td>
<td>-0.01(0.07)</td>
<td>1.0</td>
</tr>
<tr>
<td>Left MFG (BA46/9)</td>
<td>U vs. C</td>
<td>0.42 (0.07)</td>
<td>0.00005</td>
</tr>
<tr>
<td></td>
<td>D vs. C</td>
<td>0.27 (0.08)</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td>U vs. D</td>
<td>0.15(0.07)</td>
<td>0.134</td>
</tr>
<tr>
<td>Right MFG (BA46/9)</td>
<td>U vs. C</td>
<td>0.27 (0.06)</td>
<td>0.00005</td>
</tr>
<tr>
<td></td>
<td>D vs. C</td>
<td>0.31 (0.07)</td>
<td>0.00005</td>
</tr>
<tr>
<td></td>
<td>U vs. D</td>
<td>-0.04(0.07)</td>
<td>1.0</td>
</tr>
<tr>
<td>Left ATL (BA 38)</td>
<td>U vs. C</td>
<td>0.41 (0.07)</td>
<td>0.00005</td>
</tr>
<tr>
<td></td>
<td>D vs. C</td>
<td>0.17(0.08)</td>
<td>0.116</td>
</tr>
<tr>
<td></td>
<td>U vs. D</td>
<td>0.24 (0.07)</td>
<td>0.002</td>
</tr>
<tr>
<td>Right ATL (BA 38)</td>
<td>U vs. C</td>
<td>0.30 (0.07)</td>
<td>0.00005</td>
</tr>
<tr>
<td></td>
<td>D vs. C</td>
<td>0.25 (0.08)</td>
<td>0.012</td>
</tr>
<tr>
<td></td>
<td>U vs. D</td>
<td>0.05(0.07)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 4.6: Priming effects as revealed by Bonferroni multiple comparisons (standard deviations in brackets) performed on BOLD signal changes. The mean difference is significant at the 0.05 level (significant results are in bold).
4.2.2. Event related design data

4.2.2.1. Behavioral results

Mean response times (RT) and error rates were calculated for each participant as described in Chapter 3. Data from 3 subjects were removed, due to high percentage of errors (>10%). For the remaining 13 subjects, mean RT and error rates were calculated for each subject in each condition (short SOA for placebo treatment- Pla_shortSOA, long SOA for placebo treatment-Pla_longSOA, short SOA for L-Dopa treatment-DA_shortSOA, long SOA for L-Dopa treatment-DA_longSOA). Removal of errors and non-responses resulted in the exclusion of 2.5% (L-Dopa) and 1.94% (placebo) of the raw data. In order to test for general effect of L-Dopa, two t-tests were performed on overall RT and response errors. There were no significant differences in reaction time or response errors between the two drug conditions. This result is presented in Table 4.7.

<table>
<thead>
<tr>
<th></th>
<th>DA</th>
<th>Pla</th>
<th>DA</th>
<th>Pla</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT in ms (SD)</td>
<td>564</td>
<td>561</td>
<td>72 (2.5%)</td>
<td>56 (1.94%)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.65</td>
<td></td>
<td></td>
<td>0.14</td>
</tr>
</tbody>
</table>

Table 4.7: Overall response times and response errors: t-test comparisons between drug conditions.
Because the number of errors made by the remaining participants was relatively small, further analysis was performed only on response times. The average reaction times calculated for all conditions are presented in Table 4.8.

<table>
<thead>
<tr>
<th>Drug</th>
<th>L-Dopa (n=13)</th>
<th>Placebo (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>700</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>700</td>
</tr>
<tr>
<td>Semantic relationship</td>
<td>RT(SD)</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>539 (52)</td>
<td>554 (59)</td>
</tr>
<tr>
<td>D</td>
<td>560 (58)</td>
<td>575 (66)</td>
</tr>
<tr>
<td>U</td>
<td>575 (61)</td>
<td>580 (66)</td>
</tr>
</tbody>
</table>

Table 4.8: Mean response times (RT) in msec (standard deviations in brackets).

In order to assess the effects of treatment (L-dopa, placebo), SOA (short, long) and type of stimulus (C, D, U) a 2*2*3 (drug*SOA*stimulus) ANOVA was performed. A main effect for type of stimulus [F(2,554)=34.8; p<0.0005] and SOA [F(1,277)=8.2; p<0.005] were found. No other main effect or interaction was found (see Table 4.9).
Main effects and interactions | F(1,277) | p
--- | --- | ---
Drug (L-Dopa, Placebo) | 0.740 | 0.391
SOA(200ms, 700ms) | 8.196 | **0.005**
task (C, D, U) | 34.826 | **0.00005**
drug * SOA | 0.293 | 0.589
drug * task | 0.225 | 0.798
SOA * task | 0.570 | 0.566
drug * SOA * task | 1.557 | 0.212

Table 4.9: 2*2*3 ANOVA results, assessing the effect of drug, SOA and task on response times. The results are significant at the 0.05 level (results in bold).

Further 2*3 (SOA*stimulus) ANOVAs were carried our in order to assess the effect of SOA and stimulus type separately in each treatment condition. A main effect for task (i.e. C, D, U) was found again in both treatment conditions. The response times for the unrelated and distantly related word pairs were longer than those for closely related word pairs [L-Dopa: F(2,778)=21.7, p<0.0005; Placebo: F(2,778)=26.2, p<0.0005]. A main effect for SOA was also found in both treatment conditions [L-Dopa: F(1,389)=7.9, p<0.005; Placebo: F(1,389)=4.2, p<0.05]. No interaction effect was found for either drug condition. These results are summarized in Table 4.10.
Further analyses were focused on semantic priming effects, calculated as differences in RT between unrelated and closely related pairs (direct priming), unrelated and distantly related word pairs (indirect priming) and distantly related versus closely related word pairs (intermediate priming). Mean priming effects are shown in Table 4.11. The direct and intermediate semantic priming effects were significant in both treatment conditions and SOAs. The indirect semantic priming effect was significant only in the short SOA condition under L-Dopa treatment and in the long SOA condition under placebo treatment.
<table>
<thead>
<tr>
<th>Drug</th>
<th>L-Dopa</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOA</td>
<td>200</td>
<td>700</td>
</tr>
<tr>
<td>Semantic priming</td>
<td>Difference in RT (SD)</td>
<td></td>
</tr>
<tr>
<td>Direct (U-C)</td>
<td>38.75 (6.8)</td>
<td>25.19 (7.6)</td>
</tr>
<tr>
<td>Indirect (U-D)</td>
<td>15.02 (6.8)</td>
<td>4.85 (7.1)</td>
</tr>
<tr>
<td>Intermediate (D-C)</td>
<td>21.49 (6.7)</td>
<td>24.86 (7.2)</td>
</tr>
</tbody>
</table>

Table 4.11: Mean priming effects for all experimental conditions: significant differences (p<0.05) in RT (expressed in msec) are presented in bold.

4.2.2.2. Imaging results

Due to excessive motion during the scans or high percentage of errors in subject responses, 10 sets of data were discarded, resulting in the following distribution:
Pla_shortSOA: n=14; Pla_longSOA: n=15; DA_shortSOA: n=12; DA_longSOA: n=13.

For the remaining data sets, group activation maps were obtained using FSL’s cluster analysis for each of the semantic conditions (C, D, U, NW) in each drug condition (L-Dopa and Placebo) and for each type of SOA (short SOA=200ms, long SOA=700ms). The maps showing the main effect for each task are presented in Fig. 4.4 and Fig 4.5.

These revealed consistent activation areas for all types of stimuli and conditions in the LIFG (BA44/45), left posterior middle/superior temporal cortex- LpMSTC (BA 21/22), bilaterally in the MFG (BA46/9), insula, superior parietal cortex (BA7), and the
Fig 4.4: Group activation maps during the L-Dopa administration for each type of stimulus: C- closely related word pairs, D-distantly related word pairs, U-unrelated word pairs, NW–word-non-word pairs (see APPENDIX G for anatomical identification of activated areas).
Fig 4.5: Group activation maps during the placebo administration for each type of stimulus: C- closely related word pairs, D-distantly related word pairs, U-unrelated word pairs, NW-word-non-word pairs (see APPENDIX G for anatomical identification of activated areas).
ACC (BA32/24). Visual, somatosensory, motor and premotor cortices were also activated due to visual presentation of stimuli and the required motor response.

Comparisons between types of stimuli, drug condition and length of SOA were obtained by performing paired sample t-tests (direct comparisons). No main effect was found for drug or SOA on the activation maps. Also, no differences were found between the graded semantic distances: closely vs distantly, closely vs unrelated and distantly vs unrelated word pairs. However, by simple visual examination of the images (Fig. 4.4. and 4.5) it seems like the pattern is correlated with the behavioral results, i.e. less activation for closely related word pairs than for the distantly and unrelated word pairs. It is possible that these differences are too subtle to reach significance for the type of comparisons FSL performs. Therefore more complex analyses such as the ones performed for the block design (i.e. extraction of time series of individual voxels or ROIs for each data set and calculations of BOLD signal changes from these) will be necessary to reveal differences in activation between stimulus conditions and SOA, as well as drug treatment.

However, when stimuli were separated into highly related (closely related word pairs) and less related (distantly and unrelated word pairs), areas of the brain showing more activation for the less related word pairs were revealed. These are presented in Fig.4.6 and Table 4.12. The following areas of the brain were significantly more active during processing of less related words when compared to highly related words: LIFG (BA44/45), LpMSTC (BA21/22), LMFG (BA46/9), left insula, left superior parietal cortex- LPar (BA7) and the ACC (BA32/24). Also, there were significant differences in activation of visual, somato-sensory, motor and pre-motor cortices, but their significance is not understood at the moment.
Fig 4.6: Activation pattern showing regions of the brain preferentially used when processing less related word pairs when compared with highly related word pairs.
<table>
<thead>
<tr>
<th>Location</th>
<th>short SOA (200ms)</th>
<th>long SOA (700ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>drug</td>
<td>Z score</td>
</tr>
<tr>
<td>LIFG (BA44/45)</td>
<td>L-Dopa</td>
<td>3.33</td>
</tr>
<tr>
<td></td>
<td>Pla</td>
<td>2.88</td>
</tr>
<tr>
<td>LMFG (BA 46/9)</td>
<td>L-Dopa</td>
<td>4.49</td>
</tr>
<tr>
<td></td>
<td>Pla</td>
<td>3.26</td>
</tr>
<tr>
<td>LpMSTG (BA21/22)</td>
<td>L-Dopa</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Pla</td>
<td>3.74</td>
</tr>
<tr>
<td>L insula</td>
<td>L-Dopa</td>
<td>3.78</td>
</tr>
<tr>
<td></td>
<td>Pla</td>
<td>-</td>
</tr>
<tr>
<td>LPar (BA 7)</td>
<td>L-Dopa</td>
<td>4.18</td>
</tr>
<tr>
<td></td>
<td>Pla</td>
<td>3.55</td>
</tr>
<tr>
<td>ACC (BA24/32)</td>
<td>L-Dopa</td>
<td>4.04</td>
</tr>
<tr>
<td></td>
<td>Pla</td>
<td>4.02</td>
</tr>
</tbody>
</table>

Table 4.12: Regions of the brain preferentially activated during presentation of less related word pairs as compared with highly related word pairs. The coordinates are given in mm for the MNI standard brain.
4.2.3. *Comparison block design-event related design*

The semantic priming paradigm is a cognitive task for which a reaction to an unexpected stimulus is probed. Therefore it is essential that a randomization of the stimuli is carried out in order to avoid anticipation and strategy effects. We tried to achieve this in both the block and event related designs. However, due to the block’s design rules and periodicity, a complete randomization could not be attained in this case, i.e. same type of stimuli had to be presented during one block (C, D or U) and task blocks alternated with long rest blocks. However, we believe that strategic and expectation effects have been minimized by the random incorporation of non-words within blocks and by alternating the blocks containing different semantic conditions. This has been supported by the behavioral results of this study, which demonstrated a significant priming effect with this paradigm design. This type of design, also allowed us to perform more complex analyses on the imaging data, in order to reveal the effect of varying semantic distances on BOLD signal.

The complete randomization of the stimuli was realized in the event related design. This allowed us to combine all types of stimuli in one run, and to avoid the anticipation and strategy effects that the block design presentation introduced.

To determine the effect of paradigm design on brain activation during semantic priming experiments, a comparison between the activation maps obtained during the block design and event related experiments was performed. Two-sample unpaired t-tests carried out for each type of stimulus (C, D, U) revealed significant differences between the statistical maps obtained in the two experiments. The activation maps for these comparisons are presented in Fig. 4.7 and 4.8, and Table 4.13 shows the MNI coordinates...
for the peak activations in the comparison maps. The activation maps revealed the following areas of the brain as preferentially activated in the event related experiment compared to the block design experiment: the LMTC (BA21/22/37), left superior temporal gyrus –LSTG (BA22/41/42), left supramarginal gyrus –LMSG (BA 40), LPar (BA 7), ACC (BA32/24), and right angular gyrus. The right motor and pre-motor cortices were significantly more active during the block design experiment.

These results emphasize the importance of choosing the right paradigm design for an fMRI experiment. Different types of design can lead to different activation maps for the same cognitive task.
Fig 4.7: Activation pattern showing regions of the brain preferentially activated during the event related (ER) compared to block design semantic priming experiments.
Fig 4.8: Activation pattern showing regions of the brain preferentially activated during the block design compared to event related (ER) semantic priming experiments.
Table 4.13: Maximum Z-scores for regions of the brain preferentially activated during presentation of ER compared with block design semantic priming experiments. The coordinates are given in mm for the MNI standard brain.
4.2.4. Discussion

This part of the study aimed to determine the neuroanatomical substrate of semantic priming, and the effect of varying semantic distances on this substrate, using fMRI during a lexical decision task. In a pilot study, we used a block design paradigm, containing pseudo-randomized stimuli, and later on, in the pharmacological study we used an event related design, in which both the types of stimuli and the inter-trial intervals were randomized.

Behavioral measurements demonstrated a significant priming effect for all semantic distances in both the block design and the event related design. Imaging results showed that semantic priming activates a complex brain system, which includes semantic areas as well as a proposed attentional network. Similar brain areas appear to be activated during all conditions. Due to the simplicity of the design, during the block design pilot study, it was possible to examine and detect the effect of semantic distances on the magnitude of the BOLD signal. Also, differences in activation maps were obtained when the result for the block design study were compared to the event related study, revealing the importance of appropriate paradigm design selection.

Behavioral results

Response latency data was in agreement with previous findings. Namely, response times for primed stimuli were shorter than for unprimed stimuli in both the block and event related design studies. Moreover, participants showed faster responses when the targets were closely related to the prime, compared to targets distantly related to the prime. Thus, we were able to demonstrate support for the network model for the
organization of the semantic lexicon, where words are represented as nodes in the network and the distances between those nodes represent the semantic relationship between those words\textsuperscript{61-62}. The main effect found for SOA in both drug conditions, with shorter RT during a short SOA than during a long SOA paradigm suggests that, when the task is fast an “automatic” processing takes place, while when the participant has more time (long SOA) other “controlled” cognitive processes are involved resulting in a longer response time.

Although no significant main effect was found for drug condition when response latencies were analyzed, the semantic priming effects (differences in RT between unrelated and related conditions) show a different behavior. Significant direct and intermediate semantic priming effects were found in both drug treatment conditions and SOAs. These results for the direct and intermediate semantic priming are similar to previous findings\textsuperscript{62,90}. However, there is no consensus on the findings for the effect of SOA or drug on the indirect priming effects. One study found a significant indirect priming effect at short SOA in both placebo and L-Dopa conditions as well as in the long SOA under placebo condition\textsuperscript{90}. Another study found significant indirect priming at short SOA in both placebo and L-Dopa conditions. In the long SOA design, only the placebo condition revealed a significant indirect priming effect\textsuperscript{62}. Our results are yet different, showing a significant indirect semantic priming effect in the short SOA condition for L-Dopa and in the long SOA condition for placebo. Although these results are not very clear it is undeniable that L-Dopa has an effect on indirect semantic priming. This has also been shown in schizophrenic patients\textsuperscript{91,92}. Kischka et al. suggest that this validates
the role of L-Dopa as a neuromodulator, i.e. it increases the focus of activation in the semantic network, therefore restricting the access to distant nodes.

Although no strong conclusion can be drawn from these results, the significant findings of the behavioral data are: a clear distinction in reaction times for the types of stimuli and SOA and an effect of L-Dopa on the indirect semantic priming. These are important in the light of the imaging data discussed in the following.

*Imaging results*

During the lexical decision task, activation was observed in a cerebral network known to be involved in language processing and attention to the task. This network included the LIFG (BA44/45), bilateral MFG (BA46/9), parietal cortex (BA7), premotor cortex (BA6) and ACC (BA32/24), consistent with those described in previous studies\(^\text{64-67}\). In addition for the event related experiment the left posterior middle/superior temporal cortex- LpMSTC (BA 21/22) was also activated. In both block and event related design, the differences between stimulus types revealed by the behavioral data, were not found in direct comparisons of the statistical maps. However, by simple visual examination of the images (Fig. 4.4. and 4.5) it seems like the pattern is correlated with the behavioral results, i.e. less activation for closely related word pairs than for the distantly and unrelated word pairs. It is possible that these differences are too subtle to reach significance for the type of comparisons FSL performs. In the block design study, where signal time course analysis could be performed, this revealed differences in the magnitude of the BOLD signal for varying semantic distances in both hemispheres in the ATL and MFG, and also in the LIFG. The pattern for these differences was a decrease in
BOLD signal change during processing of closely related target words when compared to brain activation during the presentation of unrelated word pairs and distantly related pairs. In addition, reduced signal change was observed in distantly related pairs compared to unrelated pairs in the left anterior temporal lobe. These reductions in BOLD signal suggest a decreased neural activity possibly because the recognition threshold for the related targets is lowered by the spreading of activation from the prime. For the event related experiment more complex analyses such as the ones performed for the block design (i.e. extraction of time series of individual voxels or ROIs for each data set and calculations of BOLD signal changes from these) will be necessary to reveal differences in activation between stimulus conditions and SOA.

The critical role of the left inferior frontal gyrus (LIFG) in language processing has been widely studied and demonstrated through both lesion and neuroimaging studies. Findings suggest involvement of the LIFG in executive mechanisms such as retrieval, selection and evaluation. However, its exact role in semantic processing is still controversial. The competing hypotheses are that the role of the IFG is either retrieval of semantic information or selection among alternatives. In the present study, since selection demands were kept constant (participants had to decide if the target was a word or not, regardless of other associative parameters), the results seem to support the semantic retrieval hypothesis. The stronger activation observed for unrelated and distantly related word pair processing compared to activation during closely related word pair presentation suggests that access to these words is more demanding. The closely related target processing is facilitated by the spreading of activation from the prime,
while the unrelated or distantly related targets require a more extensive effort in order to be retrieved from semantic memory\textsuperscript{64,65,67}. This interpretation is also supported by behavioral data, as the responses to unrelated and distantly related targets are typically slower than the responses for closely related targets.

The pattern of activation in the MFG is also similar to previous findings\textsuperscript{65,67} and could be interpreted in a similar manner, namely, as the result of a search of the semantic network. Thus, the activation results in the right MFG could be interpreted as a result of retrieval effort\textsuperscript{73} which is higher for unprimed words, compared to primed words.

Three regions, the ACC, parietal cortex (BA7) and right premotor cortex (BA6), were activated during the lexical decision experiment, but not modulated by the semantic priming effect. This might reflect the involvement of attentional demands and response planning. Among the variety of functions attributed to ACC, it has been shown that this area of the brain is also engaged in events that require response selection during semantic processing\textsuperscript{109}.

The superior parietal lobe and right premotor cortex showed similar activation, not influenced by the semantic conditions. These regions have also been associated with attentional mechanisms\textsuperscript{45,66}.

In addition, in the event related study we also found activation in the posterior middle and superior temporal gyrus as described in previous literature\textsuperscript{64-67}. The involvement of these areas in phonological processing\textsuperscript{56} as well as semantic access and analysis are well known. This area of the brain is also considered to contain the acoustic/phonological representations necessary for silent reading\textsuperscript{56-59}.
Although the behavioral data for the event related study showed unequivocal differences in response to the four types of stimuli (C, D, U, NW) as well as effects of SOA (200ms and 700ms) and some drug effects, these were not found in the activation maps. Since in the block design experiment, some of these effects could be identified by signal time course analysis, they may be too subtle in the brain to be identified at low magnetic fields, in the case of the event related design. Further work involving more complex analyses as well as imaging at higher magnetic fields, is necessary to clarify these issues.

The noticeable difference in the activation maps between the event related and block design experiments lead to further analyses, i.e. direct comparisons between the activation maps in the two experiments. The results of these comparisons reflect the great importance of appropriate selection of paradigm design in functional MRI studies. The main finding was the lack of activation in the posterior temporal cortex in the block design study. Since this area of the brain has a known role in language processing \cite{64-67,69,70,80,83,84}, the results of the study omitted important information about how the brain processes language, and specific for this study how the semantic networks are distributed. This area of the brain is involved in retrieval of semantic information. The lack of activation during the block design experiment can be explained by one of the flaws of this type of experimental design: a rest period is not truly a rest state, especially for cognitive tasks. It is possible that during the rest periods the participants continued to think about the stimuli they just processed during the task block, therefore there was a continuous access to the semantic storage in the left temporal cortex. This resulted in a
cancellation of the signal in this area when the BOLD signal was calculated as a
difference between the task and rest blocks. In addition, the left parietal cortex and
anterior cingulate cortex were also more activated in the event related experiment than in
the block design. These areas are known to be involved in attention to the task. Since the
event related design consisted of a complete randomization of both the stimuli and the
inter-trial intervals, this experiment required continuous attention and increase alertness
of the participants. In comparison, the periodicity of the block design allowed participants
to anticipate the start of each task block. Therefore these areas of the brain showed
increased activation during the event related experiment when compared to the block
design. The preferential activation in the right pre-motor, motor and sensory areas, during
block design, also point out that even the selection and planning of motor responses can
be affected by the type of design used.

However, each type of design has its advantages. The block design allowed us to
further analyze the data to reveal important effects of semantic priming on brain
activation. Further, more complex analyses have to be performed for the event related
data in order to reveal these effects. The event related experiment could also benefit from
the increased sensitivity at higher magnetic fields. In conclusion, to obtain reproducible
and accurate results in the neuroimaging data, it is of fundamental importance that careful
selection of the paradigm design, considering the cognitive functions studied, has to be
accomplished.

These studies have demonstrated that graduated effects of semantic priming can
be detected with fMRI. Two different categories of brain regions activated during a
lexical decision semantic priming task have been identified. Areas known to be involved in lexical-semantic processing showed activation that was modulated by the semantic relationship between the prime and the target word. Areas in the attentional network were activated due to attentional demands of the task, but were not affected by the different semantic conditions. Our studies specifically examined the effect of varying semantic distances on brain activation during priming. Studies using alternative methodologies, such as higher magnetic fields and different statistical and deconvolution analysis of the BOLD signal, are necessary to further clarify brain behavior during semantic priming, and its modulation by either the stimulus onset asynchrony or L-Dopa. This research may serve as a tool for examining semantic networks in patient populations known to have restricted semantic networks or atypical levels of dopamine, such as cocaine withdrawal, Parkinson’s disease or schizophrenic patients.

4.3. The effects of L-dopa on the functional connectivity in the brain during language processing

4.3.1. Behavioral results

All response errors were removed and response times (RT) below 200ms were considered outliers and excluded from analysis. This resulted in the exclusion of less than 2% of the data. For the remaining data, mean response times (RT) were calculated for each participant for each of the four testing conditions, and are presented in Table 4.14. A repeated measures 2*2 (task*drug) ANOVA was carried out to detect the effect of either
drug or task on response times. A significant main effect was found for task [F(1,15)=64.5, p<0.00005] with a longer response time recorded for the semantic task (mean RT =668 msec, SD=11) as compared to the phonological task (mean RT= 602, SD=12). Neither a main effect for drug, nor interactions effects were found.

Direct comparisons between response times for each task in each of the drug/placebo treatment conditions were performed (paired sample t-test) and are presented in Table 4.15.

<table>
<thead>
<tr>
<th>Drug</th>
<th>L-Dopa</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Task</td>
<td>semantic</td>
<td>semantic</td>
</tr>
<tr>
<td></td>
<td>phonological</td>
<td>phonological</td>
</tr>
<tr>
<td>RT(SD)</td>
<td>668 (47)</td>
<td>669 (49)</td>
</tr>
<tr>
<td></td>
<td>604 (51)</td>
<td>600 (57)</td>
</tr>
</tbody>
</table>

Table 4.14: Mean response times (msec) for the two tasks in each treatment condition (SD-standard deviations).

<table>
<thead>
<tr>
<th>Drug</th>
<th>L-Dopa</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sem-Phono</td>
<td>64.3 (9.2)</td>
<td>68.6 (9.8)</td>
</tr>
<tr>
<td>t-value; p-value</td>
<td>t=6.9; p&lt;0.00005</td>
<td>t=6.9; p&lt;0.00005</td>
</tr>
</tbody>
</table>

Table 4.15: Mean differences in RT (msec) were significant in both treatment conditions(SD in brackets).
4.3.2 Imaging results-activation maps

Due to excessive motion during the scans, 4 sets of data were discarded, resulting in the following distribution: Pla_sem: n=15; Pla_phono: n=15, DA_sem: n=15, DA_phono: n=15. Group activation maps obtained using FSL’s cluster analysis reveal a pattern of activation similar to that obtained by McDermott et al\textsuperscript{80}. The pattern of brain activation associated with the processing of semantic relationship and phonological processing in the two drug conditions is shown in Fig 4.9. Relative to the baseline (fixating the cross-hair) both semantic and phonological tasks activated a set of common regions of the brain comprised of the left inferior frontal cortex- LIFG (BA44/45) extending into the premotor and motor areas, bilateral middle frontal gyrus-MFG (BA46/9), left posterior medial temporal gyrus-LpMTG (BA 21/22), left fusiform gyrus-LFUS (BA37), bilateral occipital cortex (BA 17/18/19), bilateral premotor cortex.

Differences in brain activation for the two types of processes were as follows: semantic processing preferentially activated the anterior LIFG (BA47) and posterior dorsal LIFG (BA44), bilateral MFG (BA46/9), left supramarginal gyrus (BA40) as well as LpMTG (BA21/22); phonological processing showed preferential activation in the posterior LIFC going into the premotor and motor areas (BA44/6) and the left parietal cortex-LPAR (BA7). These results agree with McDermott et al. No significant differences were found in the average maps, between drug conditions for the two different tasks.
4.3.3. Functional connectivity results

In a repeated measures 2*2*6 (task*drug*ROIpair) ANOVA, a significant main effect for task was found [$F(1,14)=6.597$, $p=0.022$], with an average correlation over both drugs and all ROI pairs, for the phonological task (mean $cc=0.506$; SE=0.06) greater than that for the semantic task (mean $cc=0.446$; SE=0.05). This is shown in Fig. 4.10.
There was no significant main effect for drug nor a significant drug*task interaction. There was also a main effect for the ROI pair \[F(5,70)=7.319, p<0.0005\]. Therefore, further 2*2 (task*drug) repeated measures ANOVAs were performed for each of the 6 ROI pairs, with the results presented in Table 4.16 and for the significant ones in Fig. 4.11, 4.12, 4.13. For the LIFG-LMTG, LIFG-LPAR, LMTG-LFUS pairs, the average correlation coefficients for both drugs were significantly greater for the phonological than for the semantic process. For the LFUS-LPAR pair a main drug effect was found, with a higher correlation coefficient across tasks, for L-Dopa than for placebo.

![Bar chart](image)

**Fig.4.10:** Mean correlation coefficient for the semantic and phonological tasks (average over all ROI pairs and drug conditions)
<table>
<thead>
<tr>
<th>ROI pair</th>
<th>Main and interaction effects</th>
<th>Mean cc (SE)</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Task (1-sem; 2-phono)</td>
<td></td>
<td>0.384 (0.062)</td>
<td>0.487 (0.076)</td>
<td>5.036</td>
</tr>
<tr>
<td>LIFG&amp;LMTG</td>
<td>Drug (1-DA; 2-Pla)</td>
<td>0.471 (0.068)</td>
<td>0.400 (0.077)</td>
<td>1.216</td>
</tr>
<tr>
<td></td>
<td>Task*Drug</td>
<td></td>
<td>1.266</td>
<td>0.280</td>
</tr>
<tr>
<td>Task (1-sem; 2-phono)</td>
<td></td>
<td>0.522 (0.047)</td>
<td>0.591 (0.055)</td>
<td>5.636</td>
</tr>
<tr>
<td>LIFG&amp;LPAR</td>
<td>Drug (1-DA; 2-Pla)</td>
<td>0.563 (0.057)</td>
<td>0.055 (0.060)</td>
<td>0.042</td>
</tr>
<tr>
<td></td>
<td>Task*Drug</td>
<td></td>
<td>0.167</td>
<td>0.689</td>
</tr>
<tr>
<td>Task (1-sem; 2-phono)</td>
<td></td>
<td>0.491 (0.058)</td>
<td>0.518 (0.066)</td>
<td>0.505</td>
</tr>
<tr>
<td>LIFG&amp;LFUS</td>
<td>Drug (1-DA; 2-Pla)</td>
<td>0.493 (0.067)</td>
<td>0.515 (0.062)</td>
<td>0.161</td>
</tr>
<tr>
<td></td>
<td>Task*Drug</td>
<td></td>
<td>0.052</td>
<td>0.822</td>
</tr>
<tr>
<td>Task (1-sem; 2-phono)</td>
<td></td>
<td>0.384 (0.058)</td>
<td>0.413 (0.074)</td>
<td>0.515</td>
</tr>
<tr>
<td>LMTG&amp;LPAR</td>
<td>Drug (1-DA; 2-Pla)</td>
<td>0.419 (0.068)</td>
<td>0.378 (0.076)</td>
<td>0.378</td>
</tr>
<tr>
<td></td>
<td>Task*Drug</td>
<td></td>
<td>0.933</td>
<td>0.350</td>
</tr>
<tr>
<td>Task (1-sem; 2-phono)</td>
<td></td>
<td>0.368 (0.065)</td>
<td>0.452 (0.067)</td>
<td>7.295</td>
</tr>
<tr>
<td>LMTG&amp;LFUS</td>
<td>Drug (1-DA; 2-Pla)</td>
<td>0.449 (0.058)</td>
<td>0.371 (0.081)</td>
<td>1.706</td>
</tr>
<tr>
<td></td>
<td>Task*Drug</td>
<td></td>
<td>0.165</td>
<td>0.691</td>
</tr>
<tr>
<td>Task (1-sem; 2-phono)</td>
<td></td>
<td>0.527 (0.058)</td>
<td>0.576 (0.054)</td>
<td>1.361</td>
</tr>
<tr>
<td>LFUS&amp;LPAR</td>
<td>Drug (1-DA; 2-Pla)</td>
<td>0.606 (0.055)</td>
<td>0.496 (0.060)</td>
<td>4.889</td>
</tr>
<tr>
<td></td>
<td>Task*Drug</td>
<td></td>
<td>0.302</td>
<td>0.591</td>
</tr>
</tbody>
</table>

Table 4.16: Results of repeated measures 2*2 ANOVAs for each ROI pair (DA-L-Dopa; Pla-placebo)
Fig. 4.11: Mean correlation coefficient for semantic and phonological tasks for the LIFG-LMTG pair (average over the two drug conditions).

Fig. 4.12: Mean correlation coefficient for semantic and phonological tasks for the LIFG-LPAR pair (average over the two drug conditions).
4.3.4. Discussion

fMRI was used to study functional connectivity associated with semantic and phonological processing and whether this is affected by L-Dopa. Brain activation maps of the semantic and phonological networks were obtained and functional connectivity was calculated as the degree of correlation between the activation time series data of two brain areas, commonly activated by the two tasks, as described in Section 2.1.6, specifically by equation (2.19).

Behavioral data, consisting of response times to the stimuli, were recorded and reflected the level of processing associated with semantic and phonological tasks: a deep level of encoding, corresponding to the semantic process, took longer to accomplish,
while the shallower level equivalent to the phonological process allowed faster responses\textsuperscript{76-78}. These were not affected by the treatment condition.

The fMRI results agreed with previous findings, showing the network of brain regions involved in semantic and phonological processes: left inferior frontal cortex-LIFG (BA44/45) extending into the premotor and motor areas, bilateral middle frontal gyrus-MFG (BA46/9), left posterior medial temporal gyrus-LpMTG (BA 21/22), left fusiform gyrus-LFUS (BA37), bilateral occipital cortex (BA 17/18/19), bilateral prefrontal cortex.

Left inferior prefrontal cortex (LIPC) constitutes a network that activates during controlled processing of both semantic and non-semantic information\textsuperscript{58,68,70-72,81,82}. The significant finding is the distinction between anterior and posterior areas of this region, which seem to be specialized for either semantic- the anterior part (BA 45/47/10) or phonological- posterior regions (BA 44/6) processing.

Posterior regions of the brain seem to be involved in retrieval of stored information such as word meaning (BA21)\textsuperscript{69,70,80,83,84} or sound (BA7/40)\textsuperscript{80,84}.

Our findings correlate with the general knowledge about the distribution of the semantic and phonological networks in the brain\textsuperscript{70,71,79-81}. In addition to this, the functional connectivity analysis demonstrated collaboration between language specific areas, when processing semantic and phonological information. Although one might expect a greater correlation of brain activity between regions of the language network in the case of a deeper level of processing (semantic in our case) than for shallow processing (phonological), our results do not confirm this hypothesis. Language areas were activated in a more synchronous manner for phonological tasks than for semantic
tasks. This may be due to the higher degree of perceptual coherence of the phonological stimuli. Furthermore, perhaps semantic tasks involve interaction between language areas as well as other representational areas, whereas phonological tasks are more restricted to interactions within language areas, and therefore demonstrate greater coherence of activation within language areas.

There were no significant drug effects on either the activation patterns or the functional connectivity, in contrast to the L-Dopa restriction of the semantic network demonstrated behaviorally in priming paradigms\textsuperscript{62,90}. Therefore, since the functional connectivity study examined L-Dopa effect on a slower, more controlled task, further work will be needed to examine the effect of this drug on functional connectivity in more rapid tasks, such as semantic priming. However, the lack of drug effect in our study could be of significance for patient populations showing atypical levels of dopamine and norepinephrine in the brain (cocaine withdrawal, schizophrenics), as well as patients using L-Dopa a treatment for their conditions (Parkinson’s disease). These results suggest that in these populations, controlled language processing will not be affected by the increased levels of dopamine in their brain.
The research presented in this dissertation consisted of the use of functional Magnetic Resonance Imaging (fMRI) to study language processing and the effect of L-Dopa on this cognitive function.

The specific goals were to: (1) Characterize the effect of L-Dopa/carbidopa on brain hemodynamics; (2) Utilize fMRI as a tool to determine the effect of semantic priming on brain activation and to assess the dopaminergic modulation of semantic priming; (3) Use fMRI as a tool to determine brain functional connectivity during language processing and the effect of L-Dopa on it.

The first aim of the project, the determination of the effect L-Dopa administration has on brain hemodynamics, was accomplished by using the measured BOLD signal in the motor and visual cortices to calculate theoretically possible changes in global baseline cerebral blood flow. The main finding for this part of the project was that L-Dopa did not affect the BOLD signal or the baseline CBF. The calculated changes in baseline CBF, were below 1% for both motor and visual cortices suggesting that the changes in global
CBF due to the drug administration were not significant and as a consequence, when the drug effect on specific cognitive functions is studied, changes in global hemodynamics would not be a factor. Thus, in the reminder of the studies we assumed that if any drug effect would be observed it would reflect the modulatory effect of L-Dopa on the specific cognitive function.

The second goal of the project was to examine the effect of semantic priming on brain activation and the modulatory effect of dopamine on this type of language processing. This part consisted of two stages: the pilot study using a block design and no pharmacological agents, and the more complex event related design study, which examined both the effect of L-Dopa and of SOA on brain activation during the semantic priming process. The goal of the pilot study was to develop a language imaging protocol at The Ohio State University and to determine if fMRI can detect different levels of semantic priming. This goal was successfully accomplished. The goal of the second stage of the experiment was to implement a different type of paradigm design, the so called event related, and to determine if the demonstrated behavioral effects of L-Dopa on the semantic priming also reflect in changes in brain activation. The activation maps obtained in this study were similar with previously reported literature, thus confirming the successful implementation of a complex paradigm design. The drug and SOA effects obtained for the behavioral studies were not reflected on the activation maps. However, due to the complexity of the design the more complex analyses of these data were not possible with the available resources. Therefore more complex analyses such as the ones performed for the block design (i.e. extraction of time series of individual voxels or ROIs
for each data set and calculations of BOLD signal changes from these) will be necessary to reveal differences in activation between stimulus conditions and SOA.

The comparison of block design and event related design for this language paradigm revealed that different selection of paradigm design in functional MRI studies could result in different activation maps. Each type of design has its advantages and drawbacks and these have to be carefully considered when planning an fMRI experiment. In our case, the simplicity of the block design allowed us to further analyze the data to reveal important effects of semantic priming on brain activation. However, the anticipation and strategy effects, as well as the long “rest” periods associated with this type of paradigm resulted in the obstruction of activation in a very important language area. In the case of the event related design, although the complete randomization of stimuli solved the problems of the block design and revealed activation in all language related areas, the more subtle effects of semantic distance, SOA and drug were obstructed. Therefore, more complex analyses have to be performed for these data in order to reveal these effects. The event related experiment could also benefit from the increased sensitivity at higher magnetic fields.

The final objective of this dissertation was to study functional connectivity in the brain during semantic and phonological processing. Also we wanted to explore whether L-Dopa also affects the interaction between language network components, as revealed by functional connectivity. Functional connectivity was calculated as the degree of temporal correlation between the activation time series data of two brain areas. The validity of our experiment was confirmed by the similarity found between the activation maps obtained in our study for the two types of language processes and those reported in
literature. The functional connectivity analysis revealed that language areas were
activated in a more synchronous manner for phonological tasks than for semantic tasks.
No drug effect was found on either the activation maps or the functional connectivity
results. This could be of significance for patient populations showing atypical levels of
catecholamines in their brain, raising the possibility that controlled language processing
will not be impaired in these individuals. This will warrant further study.

Further work will be necessary to clarify several aspects of these studies. In order
to properly determine the possible effect of L-Dopa on global brain hemodynamics,
direct measurements of cerebral blood flow, using arterial spin labeling pulse sequences,
should be carried out in future work in order to corroborate the lack of hemodynamic
effects of L-Dopa suggested by this project. In the case of the semantic priming
experiment, higher magnetic fields and more complex deconvolution analyses can be
used in order to determine if the semantic priming effects as well as the effect of L-Dopa
and SOA on them can be detected in brain activation. Furthermore, since L-Dopa is a
precursor for both dopamine and norepinephrine, more specific agonists or antagonists
(propranolol, bromocriptine) should be used in order to determine which of the
dopaminergic or noradrenergic systems is directly involved in the modulation of semantic
networks. These findings will be of significant importance for the aforementioned patient
populations affected through the catecholamine systems.
APPENDIX A

CALCULATION OF BOLD SIGNAL DEPENDENCE ON CBF, CBV AND CMRO$_2$

The BOLD signal dependence on the regional blood flow, blood volume and oxygen consumption is given by eq. (2.8).

From eq. (2.3)

$$BOLD \equiv -TE \cdot \Delta R^* = -TE(R^*_2 - R^*_2)$$

replacing $R^*_2$ and $R^*_2$ with expressions given by eq. (2.4)

$$R^*_2 \equiv K \cdot (1 - Y_a) \beta \cdot rCBV_a \quad \text{and} \quad R^*_2 \equiv K \cdot (1 - Y_r) \beta \cdot rCBV_r$$

we obtain:

$$BOLD = -TE \cdot K \cdot [(1 - Y_a) \beta \cdot rCBV_a - (1 - Y_r) \beta \cdot rCBV_r]$$

$$= -TE \cdot K \cdot rCBV_r \cdot (1 - Y_r) \beta \cdot \left[ \left( \frac{1 - Y_a}{1 - Y_r} \right)^\beta \cdot \frac{rCBV_a}{rCBV_r} - 1 \right]$$

$$= K \cdot TE \cdot rCBV_r \cdot (1 - Y_r) \beta \cdot \left[ 1 - \left( \frac{1 - Y_a}{1 - Y_r} \right)^\beta \cdot \frac{rCBV_a}{rCBV_r} \right]$$
Furthermore, from eq. (2.7):

$$CMRO_2 = C \cdot rCBF \cdot Hct \cdot (1 - Y)$$

we get:

$$(1 - Y) = \frac{CMRO_2}{C \cdot rCBF \cdot Hct}$$

therefore

$$(1 - Y_a) = \frac{CMRO_{2a}}{C \cdot rCBF_a \cdot Hct} \quad \text{and} \quad (1 - Y_r) = \frac{CMRO_{2r}}{C \cdot rCBF_r \cdot Hct}$$

$$\frac{1 - Y_a}{1 - Y_r} = \frac{CMRO_{2a}}{CMRO_{2r}} \cdot \frac{rCBF_r}{rCBF_a}$$

As a consequence, the BOLD signal can be written:

$$BOLD = K \cdot TE \cdot rCBV_r \cdot (1 - Y_r)^\beta \left[ 1 - \left( \frac{CMRO_{2a}}{CMRO_{2r}} \cdot \frac{rCBF_r}{rCBF_a} \right)^\beta \cdot \frac{rCBV_a}{rCBV_r} \right]$$

But, according to Grubb’s formula (eq. 2.5):

$$\frac{rCBV_a}{rCBV_r} = \left( \frac{rCBF_a}{rCBF_r} \right)^\alpha$$

Then

$$BOLD = K \cdot TE \cdot rCBV_r \cdot (1 - Y_r)^\beta \left[ 1 - \left( \frac{CMRO_{2a}}{CMRO_{2r}} \right)^\beta \left( \frac{rCBF_a}{rCBF_r} \right)^\beta \right]$$

or

$$BOLD = K \cdot TE \cdot rCBV_r \cdot (1 - Y_r)^\beta \left[ 1 - \left( \frac{CMRO_{2a}}{CMRO_{2r}} \right)^\beta \cdot \left( \frac{rCBF_a}{rCBF_r} \right)^{\alpha - \beta} \right]$$
APPENDIX B

CALCULATION OF ESTIMATED BOLD SIGNAL REDUCTION AS FUNCTION OF CHANGES IN BASELINE CBF DUE TO DRUG EFFECTS

The estimated BOLD signal reduction given by eq. (2.15) is calculated as follows.

Using eq. 2.8, and assuming \( \beta = 1 \), we can write:

\[
BOLD^D = K \cdot TE \cdot rCBV^D_r (1 - Y_r^D) \left[ 1 - \frac{CMRO^D_{2a}}{CMRO^D_{2r}} \left( \frac{CBF^D_a}{CBF^D_r} \right)^{\alpha - 1} \right]
\]

Similarly,

\[
BOLD^P = K \cdot TE \cdot rCBV^P_r (1 - Y_r^P) \left[ 1 - \frac{CMRO^P_{2a}}{CMRO^P_{2r}} \left( \frac{CBF^P_a}{CBF^P_r} \right)^{\alpha - 1} \right]
\]

where indices \( D \) and \( P \) refer to respectively the drug and placebo conditions, and indices \( a \) and \( r \) refer to the active and rest states.

By replacing in these equations, the CMRO\(_2\) with its expression given by eq. 2.7:

\[
CMRO_2 = C \cdot CBF \cdot Hct \cdot (1 - Y)
\]
the ratio of BOLD signal changes in the drug and placebo conditions, becomes:

\[
\frac{BOLD^D}{BOLD^P} = \frac{K \cdot TE \cdot rCBV^D_r (1 - Y^D_r)}{K \cdot TE \cdot rCBV^P_r (1 - Y^P_r)} \left[ 1 - \frac{C \cdot CBF^D_a \cdot Hct \cdot (1 - Y^D_a)}{C \cdot CBF^D_r \cdot Hct \cdot (1 - Y^D_r)} \left( \frac{CBF^D_a}{CBF^D_r} \right)^{\alpha-1} \right] \left[ 1 - \frac{C \cdot CBF^P_a \cdot Hct \cdot (1 - Y^P_a)}{C \cdot CBF^P_r \cdot Hct \cdot (1 - Y^P_r)} \left( \frac{CBF^P_a}{CBF^P_r} \right)^{\alpha-1} \right]
\]

\[
rCBV^D_r (1 - Y^D_r) \left[ 1 - \frac{CBF^D_a \cdot (1 - Y^D_a)}{CBF^D_r \cdot (1 - Y^D_r)} \left( \frac{CBF^D_a}{CBF^D_r} \right)^{\alpha-1} \right]
\]

\[
rCBV^P_r (1 - Y^P_r) \left[ 1 - \frac{CBF^P_a \cdot (1 - Y^P_a)}{CBF^P_r \cdot (1 - Y^P_r)} \left( \frac{CBF^P_a}{CBF^P_r} \right)^{\alpha-1} \right]
\]

From eq. 2.7:

\[
CMRO_{2r}^D = C \cdot CBF^D_r \cdot Hct \cdot (1 - Y^D_r) \quad \text{and} \quad CMRO_{2r}^P = C \cdot CBF^P_r \cdot Hct \cdot (1 - Y^P_r)
\]

we obtain

\[
\frac{CMRO_{2r}^D}{CMRO_{2r}^P} = \frac{CBF^D_r \cdot (1 - Y^D_r)}{CBF^P_r \cdot (1 - Y^P_r)}
\]

and assuming that CMRO2 at baseline is independent of any drug effects:

\[
\frac{CBF^D_r \cdot (1 - Y^D_r)}{CBF^P_r \cdot (1 - Y^P_r)} = 1 \Rightarrow (1 - Y^D_r) = (1 - Y^P_r) \cdot \frac{CBF^P_r}{CBF^D_r}
\]
But according to eq. 2.12, \( \Omega \) is the percent increase in baseline CBF in drug condition (relative to the placebo condition):

\[
\Omega = \frac{CBF_r^D - CBF_r^P}{CBF_r^P} = \frac{CBF_r^D}{CBF_r^P} - 1 \quad \Rightarrow \quad \frac{CBF_r^D}{CBF_r^P} = \Omega + 1
\]

and so we obtain eq. 2.13: \( (1 - Y_r^D) = (1 - Y_r^P) \cdot \frac{1}{\Omega + 1} \)

Furthermore, from Grubb’s law (eq.2.5):

\[
\frac{rCBV_{a}^D}{rCBV_r^D} = \left( \frac{CBF_{a}^D}{CBF_r^D} \right)^{\alpha} \quad \text{and} \quad \frac{rCBV_{a}^P}{rCBV_r^P} = \left( \frac{CBF_{a}^P}{CBF_r^P} \right)^{\alpha}
\]

\[
\frac{rCBV_{a}^D}{rCBV_r^D} \cdot \frac{rCBV_r^P}{rCBV_{a}^P} = \left( \frac{CBF_{a}^D}{CBF_r^D} \cdot \frac{CBF_r^P}{CBF_{a}^P} \right)^{\alpha}
\]

Considering the assumption that changes in basal CBF result in changes in baseline signal, and no changes in active state signal, i.e. \( rCBV_{a}^D = rCBV_a^P \) and \( CBF_a^D = CBF_a^P \), the previous relationship becomes:

\[
\frac{rCBV_r^P}{rCBV_r^D} = \left( \frac{CBF_r^P}{CBF_r^D} \right)^{\alpha} = \left( \frac{1}{1 + \Omega} \right)^{\alpha}
\]

and so we obtain eq. 2.14: \( rCBV_r^D = rCBV_r^P \left( 1 + \Omega \right)^{\alpha} \)
Therefore,

\[
\frac{\text{BOLD}^D}{\text{BOLD}^P} = \frac{r\text{CBV}_r^P \cdot (1 + \Omega)^{\alpha} \cdot (1 - Y_r^P) \cdot \frac{1}{\Omega + 1} \left[ 1 - \frac{(1 - Y_a^D)}{(1 - Y_r^P)} \cdot \frac{1}{\Omega + 1} \left( \frac{\text{CBF}_a^D}{\text{CBF}_r^D} \right)^{\alpha} \right]}{r\text{CBV}_r^P \cdot (1 - Y_r^P) \cdot \left[ 1 - \frac{(1 - Y_a^P)}{(1 - Y_r^P)} \left( \frac{\text{CBF}_a^P}{\text{CBF}_r^P} \right)^{\alpha} \right]}
\]

\[
= (1 + \Omega)^{\alpha - 1} \frac{\left[ 1 - \frac{(1 - Y_a^D)}{(1 - Y_r^P)} \cdot \left( \frac{\text{CBF}_a^D}{\text{CBF}_r^D} \right)^{\alpha} \right]}{\left[ 1 - \frac{(1 - Y_a^P)}{(1 - Y_r^P)} \cdot \left( \frac{\text{CBF}_a^P}{\text{CBF}_r^P} \right)^{\alpha} \right]}
\]

Using the equalities \( r\text{CBV}_a^D = r\text{CBV}_a^P \) and \( Y_a^D = Y_a^P \), this becomes:

\[
\frac{\text{BOLD}^D}{\text{BOLD}^P} = (1 + \Omega)^{\alpha - 1} \frac{\left[ 1 - \frac{(1 - Y_a^P)}{(1 - Y_r^P)} \cdot \frac{r\text{CBV}_a^D}{r\text{CBV}_r^D} \right]}{\left[ 1 - \frac{(1 - Y_a^P)}{(1 - Y_r^P)} \cdot \frac{r\text{CBV}_a^P}{r\text{CBV}_r^P} \right]}
\]
Finally, this leads to eq. 2.15, showing the estimated reduction in BOLD signal change as function of increased baseline flow due to drug effects:

\[
\frac{BOLD_D}{BOLD_P} = \frac{(1+\Omega)^{\alpha^{-1}} \cdot \frac{1-Y_a^P}{1-Y_r^P} \cdot \frac{rCBV_a^P}{rCBV_r^P} - 1 - \frac{1-Y_a^P}{1-Y_r^P} \cdot \frac{rCBV_a^P}{rCBV_r^P}}{1 - \frac{1-Y_a^P}{1-Y_r^P} \cdot \frac{rCBV_a^P}{rCBV_r^P}}
\]
APPENDIX C

EXPERIMENTAL SET-UP

Fig. C.1: Lumina LP-400 Response Pad System for stimulus presentation and response recording for fMRI (for details see www.cedrus.com).
**A** Response Pads: These are built of 100% plastic and fiber optics. They are totally inert and safe.

**B** OTEC Unit: Converts electricity to light and is connected to the pads via protected fiber optic cables.

**C** Shielded Cable (21m/65ft): Connects the OTEC unit to the penetration panel.

**D** RF Filter: Optionally installed if the penetration panel does not have a built-in filter.

**E** Shielded Cable (21m/65ft): Connects the penetration panel to the controller.

**F** Controller: Detects key presses, times them, performs TTL I/O, and connects to the host computer.

**G** Serial Cable: Connects the controller to the host computer.

**Other equipment:**

1. Control room:
   - Laptop 1 – contains SuperLab software for stimulus presentation and subject response recording
   - Laptop 2 – contains Ezlog software for scanner trigger and subject response recording.
   - 3200MP Dell Projector
   - Projector screen
   - Lumina LP-400 control box
The following can be found on the back panel of the controller (starting from the left):

- **Power Switch** - turns the system on or off.
- **9V** - the DC power adapter input.
- **Trigger Input** - accepts trigger input from the scanner (through a BNC cable) and passes it through to the serial port. The BNC cable is connected to the Master Excite Unblank J9 connector inside GE’s TPS cabinet, and collects signals for every RF pulse.
- **OTEC** - a shielded cable plugs into this connector and goes to the penetration panel of the magnet room, to connect with the response pads inside the magnet room.
- **RS-232** - a standard serial port connector links the Lumina controller to a computer running a presentation software (SuperLab).
- Accessory Connector (RJ45)-provides TTL output or input; it connects through a converter to a second computer to record trigger signal and subject responses.
- Mode-to change the serial port's software mode.
- Speed-to change the serial port's baud rate.

2. Magnet room:

- Response pads- two fiber optic response pads, each with two colored push buttons; these are built of plastic and fiber optic parts with right hand and left hand versions.
- OTEC unit converts the electrical signals to light. It is housed in an aluminum enclosure and is typically installed under the magnet.

Fig. C.3: Fiber optic response pads and OTEC unit. These are placed inside the magnet room.
APPENDIX D

VISUAL BASIC CODES FOR SORTING SUPERLAB AND EZLOG DATA FILES

Visual Basic codes for sorting the SuperLab and Ezlog data files, for the event related experiments. These scripts were created by Keith Vogt and are reproduced with his consent.

1. “DataSort”- to sort and group together the SuperLab and Ezlog data files.

Attribute VB_Name = "DataSort"
Sub DataSort()
'
' Written by Keith Vogt 2-3-2005
' Ohio State University
'
'Purpose:
'This macro reformats the EZlog fMRI data into column format and sorts
'this based on onset time. These values are then copied to the
'SuperLab data worksheet, which itself has been formatted and some
'extraneous values removed.
'
'Requirements:
'This macro is intended to be run from a 2-sheet workbook,
'with the 1st sheet being the SuperLab output and the 2nd sheet being the EZlog output.
'Additional sheets can be in the workbook, but the first two must be as stated above.
'The first sheet must be named with either "long" or "short" in the string, in order to
'calculate the formulas needed. An error message will appear if the names are incorrect.'
'---------------------------------------------------------------------------------
' Variable definitions, mostly strings
Dim ws As Worksheet
Dim wb As Workbook
Dim header1 As String
Dim header2 As String
Dim NRcheck "Can take on any "type"
' Store the names of the activated sheet and workbook for later use
Set wb = ActiveWorkbook
wb.Sheets(1).Activate "Makes sure we are on the first sheet
Set SuperLab = ActiveSheet "Stores the sheet with SuperLab output in this variable
wb.Sheets(2).Activate "switch to second sheet - the EZlog output
Set EZlog = ActiveSheet "store it also

'Initial sheet formatting
'EZlog sheet is still active from above
'Delete the rows at the bottom with variables in terms of TR
'Rows("9:13").Select
'Selection.Delete Shift:=xlUp
SuperLab.Activate "Switch back to first sheet
Range("A6:H6").Select
With Selection 'Format the heading row cells
   .HorizontalAlignment = xlCenter
   .VerticalAlignment = xlCenter
   .WrapText = True
   .Orientation = 0
   .AddIndent = False
   .IndentLevel = 0
   .ShrinkToFit = False
   .ReadingOrder = xlContext
   .MergeCells = False
End With
Columns("C:C").ColumnWidth = 6#
Range("F6").Select
Selection.Value = "Stimulus" 'Column heading
Range("F6").Select
Selection.Value = "Onset Time"
Range("G6").Select 'Size and rename new column
Selection.ColumnWidth = 10
Selection.Value = "Onset Time (ms)"
Range("H6").Select 'Size and rename new column
Selection.ColumnWidth = 10
Selection.Value = "Cal. Onset Time (s)"
Range("H7").Select
Selection.NumberFormat = "0.0"

'Want to delete all rows with a "5" in column B (for response code)
Range("B8").Select 'First row in col B where we might see a 5
NRcheck = ActiveCell.Offset(0, -1).Value 'Store event label in col A in NRcheck
Do 'loop to check for "5" until reach blank cell at bottom
   'Also want to check for the non-response possibility, where we leave one "5".
   'This is done by storing the value in the variable NRcheck and making sure
   'the cell in column A of the row below; (1 down, -1 left) from the activecell;
   'has the same value as the row we are going to delete
   Do
   NRcheck = ActiveCell.Offset(0, -1).Value 'Store event label in col A in NRcheck
   If NRcheck = "5" Then
      Selection.Delete Shift:=xlUp
   End If
Next
End Do
If ActiveCell.Value = "5" And ActiveCell.Offset(1, -1).Value = NRcheck Then
    Rows(ActiveCell.Row).Select 'select all of current row
    Selection.Delete 'delete the row
    ActiveCell.Offset(0, 1).Select 'shift right, back to col B
Else 'Only want to move down if we didn't delete anything
    ActiveCell.Offset(1, 0).Select 'shift down one row
    NRcheck = ActiveCell.Offset(0, -1).Value 'Store next event label
End If 'If-statement gets re-evaluated by looping
Loop While Not ActiveCell.Value = "" 'stop when we hit a blank cell

'Add some formulas based on the sheet name (short or long)
Range("G7").Select 'first cell in column for formula
If Not InStr(1, ActiveSheet.Name, "long") = 0 Then 'we have the long interval data
    ActiveCell.FormulaR1C1 = "=(RC[-1]-(700+RC[-3]))"
Else
    If Not InStr(1, ActiveSheet.Name, "short") = 0 Then 'we have the short interval data
        ActiveCell.FormulaR1C1 = "=(RC[-1]-(200+RC[-3]))"
    Else
        MsgBox ("Worksheet name is not labeled either long or short. Rename to identify and re-run macro.")
        Exit Sub 'Will quit macro if sheet is improperly named
End If
End If
ActiveCell.Offset(0, 1).Activate
'Calibrated Onset time is converted to seconds and 12s are subtracted for null scans
ActiveCell.FormulaR1C1 = "=(RC[-1]/1000-12)"
ActiveCell.Offset(0, -1).Activate
ActiveCell.Range("A1:B1").Select
'ActiveCell.Activate
Selection.Copy
ActiveCell.Range("A1:B171").Select
'ActiveCell.Activate
ActiveSheet.Paste
'Fill in rest of column with same formula 150X
'Selection.AutoFill Destination:=Range("G6:G176"), Type:=xlFillDefault

' Setup to copy row data from EZlog to columns in temp sheet (#3)
Sheets.Add After:=Sheets(2) 'Creates a new sheet to use as temp
EZlog.Select
Range("A5").Select 'Copy first header value and store in header1
header1 = Selection.Value
Sheets(3).Select 'select temp sheet
Range("A1").Select 'paste heading col 1 row 1
Selection.Value = header1
EZlog.Select
Range("A7").Select 'pick up second header value and store
header2 = Selection.Value
'Range("C1").Select 'paste heading col 3 row 1
'Selection.Value = header2
' Now copy first row of data
EZlog.Select
Range("A6").Select 'pick up first value of 1st row of data
Selection.Copy
Sheets(3).Select
Range("B1").Select  'paste into first row of second column
ActiveSheet.Paste

'Copy FIRST row of data from Ezlog sheet to sheet3
EZlog.Activate  'pre-loop initialization
ActiveCell.Offset(0, 1).Select 'shift one column to the right, same row (next value)
Do 'loop to copy until reach blank cell in EZlog sheet - at far right
	Selection.Copy
	Sheets(3).Select
	ActiveCell.Offset(1, 0).Select 'shift one row down, same column
	ActiveSheet.Paste
	ActiveCell.Offset(0, -1).Select 'shift one col to left to paste label
	Selection.Value = header1
	ActiveCell.Offset(0, 1).Select 'shift back to data column
EZlog.Activate
	ActiveCell.Offset(0, 1).Select 'shift one column to the right, same row
Loop While Not ActiveCell.Value = ""

' SECOND row of EZlog data copy to sheet 3 as column
' Now need to shift down to second row of data in EZlog sheet and copy those
EZlog.Activate
Range("A8").Select  'pick up first value of 2nd row of data

'Copy loop for second set of data
Do 'loop to copy until reach blank cell in sheet "os" - at far right
	Selection.Copy
	Sheets(3).Select 'switch to temp sheet
	ActiveCell.Offset(1, 0).Select 'shift one row down, same column
	ActiveSheet.Paste
	ActiveCell.Offset(0, -1).Select 'shift one col to left to paste label
	Selection.Value = header2
	ActiveCell.Offset(0, 1).Select 'shift back (to right) to data column
EZlog.Activate
	ActiveCell.Offset(0, 1).Select 'shift one column to the right, same row
Loop While Not ActiveCell.Value = "" 'until we hit a blank cell
Range("A1").Select  'cursor "home" for esthetics

'Sort the data in sheet 3 by time
Sheets(3).Select 'switch to sheet3
Range(Selection, Cells(1)).Select 'select cells from end (should be active) to A1
Selection.Sort Key1:=Range("B1"), Order1:=xlAscending, Header:=xlGuess, _, OrderCustom:=1, MatchCase:=False, Orientation:=xlTopToBottom, _, DataOption1:=xlSortNormal

'Copy sorted values to SuperLab sheet
Selection.Copy 'Sorted values are still selected
SuperLab.Activate  'switch to Superlab data sheet and..
Range("E8").Select 'go to first row under the headers in appropriate column
ActiveSheet.Paste  'put 'em down

End Sub 'That's all folks
2. “DataMove”- script used to sort the events and their onset times by type of event.

Attribute VB_Name = "DataMove"
Sub DataMove()
  ' Written by Keith Vogt 2-11-2005
  ' Ohio State University
  
  'Purpose:
  ' This macro should divide the sorted and edited data into groups (in new sheets)
  ' based on the type of word shown (stimulus), using the following codes:
  ' CR = closely related
  ' DR = distantly related
  ' UR = unrelated
  ' NW = non-word
  
  'Requirements:
  'Designed to be run after the macro DataSort, which condenses and
  ' formats the data into one sheet, the first in the workbook.
  'Manual alignment of the Trial Name and timing data must also be done
  ' before running this Macro.
  'This macro requires that the workbook have (at least)3 sheets in it
  ' with the first being the source data for the data to be divided,
  ' originally the Superlab sheet modified by the macro "DataMove"
  '
  '-------------------------------------------------------------------------------------------------

  'Insert new sheets for the separated data, after the 3rd sheet
  Sheets.Add After:=Sheets(1) 'insert a sheet after sheet 3

  'Copy the headers to sheet 3
  Sheets(1).Activate
  Range("A6:H6").Select 'headers
  Selection.Copy
  Sheets(4).Select 'new sheet
  ActiveSheet.Paste
  Range("A2").Select 'want this cell active to start

  'Make 3 more copies of this sheet with the headers
  For i = 1 To 3 'just loop 3 times
    Sheets(4).Copy Before:=Sheets(4)
  Next i

  'Rename the Sheets to differentiate them
  Sheets(4).Name = "CR" 'closely related words stimulus
  Sheets(5).Name = "DR" 'distantly related
  Sheets(6).Name = "UR" 'unrelated
  Sheets(7).Name = "NW" 'non-word

  'Copy data to the appropriate sheet based on the Trial label value
  'for the row stored in column A of first sheet (formatted Superlab output)
Sheets(1).Activate  'switch to source sheet (first one)
Range("A6").Select  'starting cell
Do  'loop through all rows until we reach blank cell at bottom
    If Not InStr(1, ActiveCell.Value, "C") = 0 Then 'closely related
        'copy the row to the sheet "CR"
        'first, select the cells in the row relative to the first col
        ActiveCell.Range("A1:H1").Select
        Selection.Copy
        Sheets("CR").Select 'Switch to target sheet
        ActiveSheet.Paste  'Paste in appropriate sheet
        ActiveCell.Offset(1, 0).Select 'Shift down one cell for next empty row
        Sheets(1).Select  'Switch back to source sheet
        Application.CutCopyMode = False 'Unselect the copy function
    End If

    If Not InStr(1, ActiveCell.Value, "D") = 0 Then 'distantly related
        'copy the row to the sheet "DR"
        ActiveCell.Range("A1:H1").Select 'select important cells in row
        Selection.Copy
        Sheets("DR").Select 'Switch to target sheet
        ActiveSheet.Paste  'Paste in appropriate sheet
        ActiveCell.Offset(1, 0).Select 'Shift down one cell for next empty row
        Sheets(1).Select 'Switch back to source sheet
        Application.CutCopyMode = False 'Unselect the copy function
    End If

    If Not InStr(1, ActiveCell.Value, "U") = 0 Then 'unrelated
        'copy the row to the sheet "UR"
        ActiveCell.Range("A1:H1").Select 'select important cells in row
        Selection.Copy
        Sheets("UR").Select 'Switch to target sheet
        ActiveSheet.Paste  'Paste in appropriate sheet
        ActiveCell.Offset(1, 0).Select 'Shift down one cell for next empty row
        Sheets(1).Select 'Switch back to source sheet
        Application.CutCopyMode = False 'Unselect the copy function
    End If

    If Not InStr(1, ActiveCell.Value, "NW") = 0 Then 'a non-word
        'copy the row to the sheet "NW"
        ActiveCell.Range("A1:H1").Select 'select important cells in row
        Selection.Copy
        Sheets("NW").Select 'Switch to target sheet
        ActiveSheet.Paste  'Paste in appropriate sheet
        ActiveCell.Offset(1, 0).Select 'Shift down one cell for next empty row
        Sheets(1).Select 'Switch back to source sheet
        Application.CutCopyMode = False 'Unselect the copy function
    End If

    ActiveCell.Offset(1, 0).Select 'shift down one row for next value
    'Then go back and re-evaluate the "If" statements unless...
    Loop While Not ActiveCell.Value = "" 'stop when we hit a blank cell

'Tidy up at the end by moving cursor "home" on the sheets we used
Range("A6").Select
Sheets("CR").Select
Range("A2").Select
Sheets("DR").Select
Range("A2").Select
Sheets("UR").Select
Range("A2").Select
Sheets("NW").Select
Range("A2").Select

End Sub 'The End
APPENDIX E

LISTS OF WORD PAIRS USED IN THE SEMANTIC PRIMING EXPERIMENTS

1. **Block design experiment:**

<table>
<thead>
<tr>
<th>Closely related word pairs</th>
<th>Distantly related word pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. city-state</td>
<td>1. woman-husband</td>
</tr>
<tr>
<td>2. violin-string</td>
<td>2. cheetah-slow</td>
</tr>
<tr>
<td>3. leaf-maple</td>
<td>3. table-sitting</td>
</tr>
<tr>
<td>4. apple-seed</td>
<td>4. car-coal</td>
</tr>
<tr>
<td>5. judge-court</td>
<td>5. spider-silk</td>
</tr>
<tr>
<td>6. quarter-dime</td>
<td>6. crystal-window</td>
</tr>
<tr>
<td>7. soldier-cadet</td>
<td>7. alligator-feather</td>
</tr>
<tr>
<td>8. face-moustache</td>
<td>8. herb-root</td>
</tr>
<tr>
<td>9. birthday-party</td>
<td>9. kennel-bone</td>
</tr>
<tr>
<td>10. bed-pillow</td>
<td>10. staple-cut</td>
</tr>
<tr>
<td>11. clean-sponge</td>
<td>11. crayon-print</td>
</tr>
<tr>
<td>12. fire-ash</td>
<td>12. stallion-donkey</td>
</tr>
<tr>
<td>13. bird-beak</td>
<td>13. rocket-crater</td>
</tr>
<tr>
<td>14. can-lid</td>
<td>14. beggar-wealth</td>
</tr>
<tr>
<td>15. warlock-witch</td>
<td>15. funeral-life</td>
</tr>
<tr>
<td>16. daisy-tulip</td>
<td>16. boss-salary</td>
</tr>
<tr>
<td>17. bone-muscle</td>
<td>17. knight-moat</td>
</tr>
<tr>
<td>18. doctor-nurse</td>
<td>18. camera-souvenir</td>
</tr>
<tr>
<td>19. wine-liquor</td>
<td>19. wallet-purchase</td>
</tr>
<tr>
<td>20. mountain-climb</td>
<td>20. day-dark</td>
</tr>
<tr>
<td>21. water-ocean</td>
<td>21. olive-vinegar</td>
</tr>
<tr>
<td>22. coffee-bean</td>
<td>22. book-reporter</td>
</tr>
<tr>
<td>23. dart-target</td>
<td>23. sun-rainbow</td>
</tr>
<tr>
<td>24. frame-portrait</td>
<td>24. lungs-smoking</td>
</tr>
<tr>
<td>25. turtle-slow</td>
<td>25. sidewalk-highway</td>
</tr>
</tbody>
</table>
Unrelated word pairs

1. crazy-bench
2. worry-pot
3. truck-sieve
4. wig-candy
5. juice-chair
6. bamboo-turkey
7. cognac-glue
8. stork-purple
9. beard-termite
10. salad-dragon
11. tuna-cotton
12. locust-tandem
13. stupor-blot
14. haircut-crawl
15. prison-flag
16. cramp-time
17. corn-tank
18. block-horn
19. tale-run
20. opening-cloth
21. barrel-star
22. knoll-pork
23. clam-rubber
24. dance-skull
25. pond-wire
26. oyster-soccer
27. glacier-stamp
28. stitch-cracker
29. quarter-van
30. waffle-twins
31. clean-bacon
32. brick-candle
33. picture-candy
34. vanilla-headache
35. helmet-spray
36. ocean-chicken
37. crumb-bicycle
38. terrace-paper
39. anchor-bulb
40. country-teardrop
41. hurricane-cheese
42. cabinet-marsh
43. trumpet-plate
44. marble-box
45. calendar-cushion
46. stereo-bridge
47. scissors-net
48. cable-flower
49. moose-cotton
50. radio-soup

Non-word pairs

1. crate-sharl
2. light-dempt
3. henna-stonfer
4. grayish-whirfen
5. late-ophark
6. orange-theral
7. temple-sterkel
8. then-bushtek
9. pill-nerbew
10. laurel-stenke
11. timber-roily
12. neck-kanstiff
13. bottle-sturgo
14. vase-nirstuck
15. café-wough
16. triangle-sleaper
17. leap-hamare
18. airport-logupe
19. brick-yornal
20. pants-creisty
21. goldfish-muslift
22. pointy-blooper
23. gnome-shrump
24. horse-crewns
25. hands-helound
26. fluid-pallot
27. iron-crawliff
28. sterile-avrand
29. sticker-mordund
30. newspaper-blit
31. pickle-willfrond
32. postcard-labritir
2. Event related design experiment

**List 1**

<table>
<thead>
<tr>
<th>Closely related word pairs</th>
<th>Distantly related word pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. outside – inside</td>
<td>1. anvil – nail</td>
</tr>
<tr>
<td>2. farmer – field</td>
<td>2. bee – lazy</td>
</tr>
<tr>
<td>3. head – neck</td>
<td>3. eye – smell</td>
</tr>
<tr>
<td>4. pie – pastry</td>
<td>4. rod - thick</td>
</tr>
<tr>
<td>5. leg – arm</td>
<td>5. banana – jungle</td>
</tr>
<tr>
<td>6. storm – thunder</td>
<td>6. beer – grapes</td>
</tr>
<tr>
<td>7. castle – knight</td>
<td>7. flower – taste</td>
</tr>
<tr>
<td>8. roof – tile</td>
<td>8. square – algebra</td>
</tr>
<tr>
<td>9. mist – fog</td>
<td>9. ice – warm</td>
</tr>
<tr>
<td>10. near – far</td>
<td>10. fork – cut</td>
</tr>
<tr>
<td>11. paddle – boat</td>
<td>11. hand – step</td>
</tr>
<tr>
<td>12. bath – soap</td>
<td>12. hard – wool</td>
</tr>
<tr>
<td>15. tenant – rent</td>
<td>15. honey – bitter</td>
</tr>
<tr>
<td>17. hate – love</td>
<td>17. cat – trap</td>
</tr>
<tr>
<td>18. coffee – cup</td>
<td>18. chalk – black</td>
</tr>
<tr>
<td>19. cinema – movie</td>
<td>19. crystal – hazy</td>
</tr>
<tr>
<td>20. piano – key</td>
<td>20. buy – cart</td>
</tr>
<tr>
<td>22. ladder – rung</td>
<td>22. nose – hear</td>
</tr>
<tr>
<td>23. reading – writing</td>
<td>23. nest – feather</td>
</tr>
<tr>
<td>24. air – breathe</td>
<td>24. web – insect</td>
</tr>
<tr>
<td>25. painter – brush</td>
<td>25. paint – window</td>
</tr>
<tr>
<td>26. morning – evening</td>
<td>26. priest – tower</td>
</tr>
<tr>
<td>27. mouth – kiss</td>
<td>27. quick – snail</td>
</tr>
<tr>
<td>28. mother – father</td>
<td>28. rough – silk</td>
</tr>
<tr>
<td>29. nun – monk</td>
<td>29. rain – dry</td>
</tr>
<tr>
<td>30. carrot – rabbit</td>
<td>30. string – needle</td>
</tr>
</tbody>
</table>
Unrelated word pairs

1. anchor – type
2. annoy – pearl
3. path – fruit
4. balcony – earring
5. ask – rooster
6. pencil – batch
7. map – teeth
8. lady – burrow
9. ivy – towel
10. fern – bus
11. rock – cable
12. window – faculty
13. tuxedo – journey
14. singing – cut
15. bog – history
16. team – frog
17. guitar – gravel
18. glass – flag
19. fire – scales
20. fight – case
21. box – campus
22. knock – stretch
23. button – sheep
24. cow – book
25. body – table
26. envy – lid
27. jelly – toaster
28. rest – grain
29. bill – quiet
30. empire – look

Non-word pairs

1. socks - plood
2. number - killp
3. drawer - cranse
4. kettle – bilde
5. fire – serle
6. moth - wesal
7. machine - ropler
8. rainbow - voiker
9. cycle - priscal
10. boat - derling
11. sled - poilter
12. story - koelth
13. outlet - sutper
14. street - juilto
15. ship - feilon
16. rocket - munkor
17. train - breelo
18. cold - laudep
19. people - hirtle
20. bar - chancem
21. time – nimen
22. goat – diman
23. hunter – kiol
24. wreck – guffan
25. trick – cresde
26. bike – finole
27. pretend – grelled
28. tissue – convus
29. change – polin
30. whisper – nakode
31. crate-sharl
32. light-dempt
33. bottle-stonfer
34. gray-whirfen
35. late-ophark
36. orange-theral
37. temple-sterkel
38. theatre-bushtek
39. pill-nerbew
40. lamps-stenke
41. timber-roilly
42. neck-kanstiff
43. phone-sturgo
44. inside-kad
45. diner-wough
46. triangle-sleper
47. leap-hamare
48. airport-logupe
49. brick-yornal
50. pants-creisty
51. jail-buc
52. fish-muslift
53. flakes-ghape
54. dagger-rutten
55. planet-ega
<table>
<thead>
<tr>
<th>Closely related word pairs</th>
<th>Distantly related word pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. arrow – bow</td>
<td>1. feather-heavy</td>
</tr>
<tr>
<td>2. horse – ride</td>
<td>2. summer – snow</td>
</tr>
<tr>
<td>3. mail – letter</td>
<td>3. spinach – red</td>
</tr>
<tr>
<td>4. salt – sugar</td>
<td>4. mow - green</td>
</tr>
<tr>
<td>5. student – teacher</td>
<td>5. bull – milk</td>
</tr>
<tr>
<td>6. eggs – bacon</td>
<td>6. day – dark</td>
</tr>
<tr>
<td>7. aunt – uncle</td>
<td>7. valley – high</td>
</tr>
<tr>
<td>8. table – top</td>
<td>8. dove – war</td>
</tr>
<tr>
<td>9. rough – smooth</td>
<td>9. tea – bean</td>
</tr>
<tr>
<td>10. vacation – travel</td>
<td>10. soft – steel</td>
</tr>
<tr>
<td>11. hay – barn</td>
<td>11. week – night</td>
</tr>
<tr>
<td>12. wood – lumber</td>
<td>12. desert – beach</td>
</tr>
<tr>
<td>13. cheese – cake</td>
<td>13. lemon – sweet</td>
</tr>
<tr>
<td>14. window – door</td>
<td>14. dwarf – big</td>
</tr>
<tr>
<td>15. rose – thorn</td>
<td>15. stamp – send</td>
</tr>
<tr>
<td>16. clock – hour</td>
<td>16. lock – chain</td>
</tr>
<tr>
<td>17. grass – mulch</td>
<td>17. chair – stand</td>
</tr>
<tr>
<td>18. week – month</td>
<td>18. peel – juice</td>
</tr>
<tr>
<td>19. shoes – running</td>
<td>19. wheel – square</td>
</tr>
<tr>
<td>20. sink – wash</td>
<td>20. glasses – write</td>
</tr>
<tr>
<td>22. violin – string</td>
<td>22. dog – mouse</td>
</tr>
<tr>
<td>23. apple – orange</td>
<td>23. woman – husband</td>
</tr>
<tr>
<td>24. judge – court</td>
<td>24. cheetah – slow</td>
</tr>
<tr>
<td>25. quarter – dime</td>
<td>25. car – coal</td>
</tr>
<tr>
<td>26. soldier – cadet</td>
<td>26. spider – silk</td>
</tr>
<tr>
<td>27. birthday – party</td>
<td>27. crystal – window</td>
</tr>
<tr>
<td>28. bed – pillow</td>
<td>28. alligator – feather</td>
</tr>
<tr>
<td>29. fire – flame</td>
<td>29. cat – bone</td>
</tr>
<tr>
<td>30. spells – witch</td>
<td>30. stapler – cut</td>
</tr>
</tbody>
</table>
### Unrelated word pairs

1. roll – cream
2. chess – stair
3. soul – spoon
4. pig – quarter
5. sesame – convict
6. play – barrel
7. stone – printer
8. cap – star
9. hop – knit
10. hit – river
11. gas – warning
12. pot – news
13. chest – sow
14. weed – winner
15. vase – coat
16. plant – stadium
17. sun – mirror
18. file – lung
19. disk – cat
20. comb – plane
21. smoke – watch
22. tissue – wire
23. floor – pencil
24. gloves – money
25. thief – bath
26. key – ceiling
27. heat – table
28. course – chimney
29. horn – plate
30. town – bite
31. juice – heard
32. shop – loard
33. tractor – willad
34. nurse – drilly
35. wife – butine
36. shelf – ritane
37. walk – arrsen
38. help – graide
39. police – bugde
40. soup – foadle
41. pickle-wilfrond
42. post-labriti
43. honey-holsch
44. lead-pentap
45. speech-stox
46. camera-tilechy
47. towel-clishaw
48. drawer-rulle
49. stain-critran
50. frog-tipcher
51. pencil-donce
52. laugh-blech
53. paper-diract
54. absence-ges
55. stain-critan

### Non-word pairs

1. mind – quarelp
2. car - knawny
3. slot – beeth
4. chant – gleath
5. buy - kurther
6. brick - drickal
7. phone - erokle
8. boil - vamtrten
9. height - mothlop
10. shallow – naxer
11. lamb-jugge
12. disk-chist
13. account-ket
14. lead-keddny
15. brain-gerls
16. book-carpon
17. cop-pirfict
18. towel-forvire
19. mansion-phese
20. lady-danter
List3

Closely related word pairs

<table>
<thead>
<tr>
<th>1.</th>
<th>daisy-tulip</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>bone-muscle</td>
</tr>
<tr>
<td>3.</td>
<td>doctor-nurse</td>
</tr>
<tr>
<td>4.</td>
<td>wine-liquor</td>
</tr>
<tr>
<td>5.</td>
<td>hike-climb</td>
</tr>
<tr>
<td>6.</td>
<td>ocean-beach</td>
</tr>
<tr>
<td>7.</td>
<td>tea-coffee</td>
</tr>
<tr>
<td>8.</td>
<td>dart-target</td>
</tr>
<tr>
<td>9.</td>
<td>frame-photo</td>
</tr>
<tr>
<td>10.</td>
<td>turtle-slow</td>
</tr>
<tr>
<td>11.</td>
<td>bath-water</td>
</tr>
<tr>
<td>12.</td>
<td>sleep-bed</td>
</tr>
<tr>
<td>13.</td>
<td>shoes-socks</td>
</tr>
<tr>
<td>14.</td>
<td>bitter-sweet</td>
</tr>
<tr>
<td>15.</td>
<td>black-white</td>
</tr>
<tr>
<td>16.</td>
<td>light-dark</td>
</tr>
<tr>
<td>17.</td>
<td>cold-hot</td>
</tr>
<tr>
<td>18.</td>
<td>blue-sky</td>
</tr>
<tr>
<td>19.</td>
<td>boy-girl</td>
</tr>
<tr>
<td>20.</td>
<td>long-short</td>
</tr>
<tr>
<td>21.</td>
<td>thief-steal</td>
</tr>
<tr>
<td>22.</td>
<td>bread-butter</td>
</tr>
<tr>
<td>23.</td>
<td>carpet-rug</td>
</tr>
<tr>
<td>24.</td>
<td>street-car</td>
</tr>
<tr>
<td>25.</td>
<td>chair-table</td>
</tr>
<tr>
<td>26.</td>
<td>flower-stem</td>
</tr>
<tr>
<td>27.</td>
<td>child-mother</td>
</tr>
<tr>
<td>28.</td>
<td>cottage-house</td>
</tr>
<tr>
<td>29.</td>
<td>baby-cry</td>
</tr>
<tr>
<td>30.</td>
<td>spider-insect</td>
</tr>
</tbody>
</table>

Distantly related word pairs

<p>| 1.  | crayon-print |
| 2.  | stallion-donkey |
| 3.  | sun-polish |
| 4.  | beggar-wealth |
| 5.  | funeral-life |
| 6.  | knight-moat |
| 7.  | camera-painting |
| 8.  | wallet-purchase |
| 9.  | sweep-ceiling |
| 10. | olive-vinegar |
| 11. | book-reporter |
| 12. | heart-breathe |
| 13. | cow-eggs |
| 14. | eat-liquid |
| 15. | lettuce-fruit |
| 16. | airplane-drive |
| 17. | silver-fish |
| 18. | letter-count |
| 19. | chair-stand |
| 20. | danger-courage |
| 21. | bath-dirty |
| 22. | bed-awake |
| 23. | snow-black |
| 24. | bread-drink |
| 25. | peanut-toast |
| 26. | ocean-small |
| 27. | cabbage-fruit |
| 28. | ceiling-carpet |
| 29. | hospital-teacher |
| 30. | earth-square |</p>
<table>
<thead>
<tr>
<th>Unrelated word pairs</th>
<th>Non-word pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. town – bite</td>
<td>1. sky – wirte</td>
</tr>
<tr>
<td>2. bag – drawer</td>
<td>2. blue – drella</td>
</tr>
<tr>
<td>3. virus – blouse</td>
<td>3. pool – rumend</td>
</tr>
<tr>
<td>4. tennis – sticker</td>
<td>4. foot – loiner</td>
</tr>
<tr>
<td>5. noise – without</td>
<td>5. soil – junepe</td>
</tr>
<tr>
<td>6. antenna – liver</td>
<td>6. stars – nighy</td>
</tr>
<tr>
<td>7. show – crisp</td>
<td>7. throw – buone</td>
</tr>
<tr>
<td>8. speaker – trophy</td>
<td>8. handle – minell</td>
</tr>
<tr>
<td>9. yacht – clumsy</td>
<td>9. water – shuille</td>
</tr>
<tr>
<td>10. blush – nice</td>
<td>10. speaker – trune</td>
</tr>
<tr>
<td>11. tooth – father</td>
<td>11. lunch – creath</td>
</tr>
<tr>
<td>12. bug – balloon</td>
<td>12. pattern – plean</td>
</tr>
<tr>
<td>15. brush – minute</td>
<td>15. picture – ves</td>
</tr>
<tr>
<td>16. squash – gray</td>
<td>16. clone – minkle</td>
</tr>
<tr>
<td>17. kind – poster</td>
<td>17. hair – cho</td>
</tr>
<tr>
<td>18. water – stapler</td>
<td>18. lemon – asdente</td>
</tr>
<tr>
<td>19. ink – boil</td>
<td>19. pick – yuille</td>
</tr>
<tr>
<td>20. kettle – prince</td>
<td>20. music – hunde</td>
</tr>
<tr>
<td>21. porter – yeast</td>
<td>21. label-feirry</td>
</tr>
<tr>
<td>22. switch – zebra</td>
<td>22. lace -bloomes</td>
</tr>
<tr>
<td>23. spring – cut</td>
<td>23. ache-dacatar</td>
</tr>
<tr>
<td>24. class – rust</td>
<td>24. daisy-pifot</td>
</tr>
<tr>
<td>25. chase – point</td>
<td>25. dam-sabor</td>
</tr>
<tr>
<td>27. city – paddle</td>
<td>27. cabin-fraence</td>
</tr>
<tr>
<td>28. rat – captain</td>
<td>28. blast-tafent</td>
</tr>
<tr>
<td>29. ship – wart</td>
<td>29. fish-urgate</td>
</tr>
<tr>
<td>30. board – pair</td>
<td>30. games-peaner</td>
</tr>
<tr>
<td></td>
<td>31. keys-taquit</td>
</tr>
<tr>
<td></td>
<td>32. bone-dorr</td>
</tr>
<tr>
<td></td>
<td>33. flower-taquit</td>
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<tr>
<td></td>
<td>34. vase-nirstuck</td>
</tr>
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<td></td>
<td>35. report-technich</td>
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<td></td>
<td>36. cage-sirtem</td>
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<td></td>
<td>37. sugar-weith</td>
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<td></td>
<td>38. tablet-friad</td>
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<td></td>
<td>39. help -greced</td>
</tr>
<tr>
<td></td>
<td>40. victim-rase</td>
</tr>
<tr>
<td></td>
<td>41. joy-pattrrel</td>
</tr>
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<td></td>
<td>42. display -bllan</td>
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<td></td>
<td>43. system-vullcon</td>
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<td>44. camp-secrrep</td>
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<td>45. record-thoft</td>
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<td>46. gift-tunnis</td>
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<td></td>
<td>47. camel-runnire</td>
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<td></td>
<td>48. tiger-woppen</td>
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<td>49. sample-flete</td>
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<td>50. wall-thape</td>
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<td></td>
<td>51. rat-hallder</td>
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<td></td>
<td>52. tray-edgey</td>
</tr>
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<td></td>
<td>53. river-waddew</td>
</tr>
<tr>
<td></td>
<td>54. harbor-drem</td>
</tr>
<tr>
<td></td>
<td>55. package-hopi</td>
</tr>
</tbody>
</table>
56. gnome-shrump
57. case-vocted
58. score-totul
59. fabric-romed
60. garage-rab

<table>
<thead>
<tr>
<th>Closely related word pairs</th>
<th>Distantly related word pairs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. music-sound</td>
<td>1. wheel – square</td>
</tr>
<tr>
<td>2. sleep-dream</td>
<td>2. hand-toes</td>
</tr>
<tr>
<td>3. eagle-bird</td>
<td>3. grass-blue</td>
</tr>
<tr>
<td>4. grass- green</td>
<td>4. hammer-sharp</td>
</tr>
<tr>
<td>5. needle-syringe</td>
<td>5. thorn-garden</td>
</tr>
<tr>
<td>6. guns-shoot</td>
<td>6. gym- inactive</td>
</tr>
<tr>
<td>7. hard-soft</td>
<td>7. bright-planet</td>
</tr>
<tr>
<td>8. joy-sorrow</td>
<td>8. lion- weak</td>
</tr>
<tr>
<td>9. now-never</td>
<td>9. loud-whisper</td>
</tr>
<tr>
<td>10. jump-skip</td>
<td>10. memory-heart</td>
</tr>
<tr>
<td>11. square-round</td>
<td>11. poet- music</td>
</tr>
<tr>
<td>12. justice-peace</td>
<td>12. needle-blunt</td>
</tr>
<tr>
<td>13. lift-weight</td>
<td>13. river-still</td>
</tr>
<tr>
<td>14. speak-listen</td>
<td>14. sheep-cotton</td>
</tr>
<tr>
<td>15. numbers-letters</td>
<td>15. velvet-rough</td>
</tr>
<tr>
<td>16. sour-lemon</td>
<td>16. taste-nose</td>
</tr>
<tr>
<td>17. lion-tiger</td>
<td>17. stove-freeze</td>
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<td>16. tuna-cotton</td>
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<td>17. locust-caravan</td>
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<td>28. people-regget</td>
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<td>19. haircut-crawl</td>
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<tr>
<td>2. tail – zarke</td>
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</tr>
<tr>
<td>3. leaf – theane</td>
<td></td>
</tr>
<tr>
<td>4. dry – loke</td>
<td></td>
</tr>
<tr>
<td>5. piano – numben</td>
<td></td>
</tr>
<tr>
<td>6. binder – voiled</td>
<td></td>
</tr>
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<td>7. truck – podie</td>
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<tr>
<td>8. slip – moine</td>
<td></td>
</tr>
<tr>
<td>9. hanger – roothe</td>
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</tr>
<tr>
<td>10. dish – briled</td>
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56. ribbon-tok
57. drink-segen
58. panic-ruch
59. hobby-druge
60. golf-passge
LISTS OF WORDS USED IN THE FUNCTIONAL CONNECTIVITY EXPERIMENTS

Semantic Task

List1=sem1

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<th>Block1</th>
<th>Block2</th>
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<tbody>
<tr>
<td><strong>Cue:</strong> LAW</td>
<td><strong>Cue:</strong> DIET</td>
</tr>
<tr>
<td><strong>Related:</strong> attorney, enforce, criminal, lawyer, court, legal, officer, justice, police, order</td>
<td><strong>Related:</strong> thin, obese, weight, calorie, slim, pudgy, slender, skinny, lean, chubby</td>
</tr>
<tr>
<td><strong>Unrelated:</strong> shoe, bottle, car, picture, pool</td>
<td><strong>Unrelated:</strong> chair, key, glasses, clock, tissue</td>
</tr>
</tbody>
</table>
Block3

Cue: **COLD**

Related: hot
        warm
        winter
        ice
        frigid
        chilly
        heat
        freeze
        shiver
        frost

Unrelated: print
           wheel
           mouse
           book
           draw

Block4

Cue: **FRUIT**

Related: apple
        orange
        citrus
        ripe
        pear
        banana
        cherry
        basket
        juice
        salad

Unrelated: hill
           friend
           needle
           coat
           steal

List2=sem2

Block1

Cue: **DOCTOR**

Related: health
        illness
        nausea
        cough
        virus
        disease
        medicine
        fever
        hospital
        clinic

Unrelated: eagle
           skirt
           rabbit
           wheel
           bridge

Block2

Cue: **SMOKE**

Related: cigarette
        pollution
        ashes
        cigar
        chimney
        fire
        tobacco
        pipe
        flames
        inhale

Unrelated: rain
           board
           study
           town
           ocean
<table>
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<th>Block4</th>
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</thead>
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<td><strong>VEHICLE</strong></td>
<td><strong>CLOTHES</strong></td>
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<td><strong>Related</strong></td>
<td><strong>Related:</strong></td>
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<td>blouse</td>
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<tr>
<td>drive</td>
<td>sleeves</td>
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<td>jeep</td>
<td>pants</td>
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<td>tie</td>
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<td>collar</td>
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<td>highway</td>
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### Phonological Task

**List1=phonol**

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<td>root</td>
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<td>tribute</td>
</tr>
<tr>
<td></td>
<td>suit</td>
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<td></td>
<td>salute</td>
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<td></td>
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<td></td>
<td>pursuit</td>
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**Rhyme:** brute
cute
boot
root
tribute
suit
salute
dispute
pursuit
compute

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<tr>
<td></td>
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<tr>
<td></td>
<td>dog</td>
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**Block2**

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<td></td>
<td>crack</td>
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<td>back</td>
</tr>
<tr>
<td></td>
<td>stack</td>
</tr>
<tr>
<td></td>
<td>snack</td>
</tr>
<tr>
<td></td>
<td>slack</td>
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<tr>
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<td>plaque</td>
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<tr>
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<td>jack</td>
</tr>
<tr>
<td></td>
<td>hack</td>
</tr>
<tr>
<td></td>
<td>lack</td>
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**Rhyme:** track
crack
back
stack
snack
slack
plaque
jack
hack
lack

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<tr>
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**Block3**

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<td></td>
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<tr>
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<td>where</td>
</tr>
<tr>
<td></td>
<td>hair</td>
</tr>
<tr>
<td></td>
<td>swear</td>
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<tr>
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</tr>
<tr>
<td></td>
<td>bear</td>
</tr>
<tr>
<td></td>
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<tr>
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<td>scare</td>
</tr>
<tr>
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**Rhyme:** air
flair
where
hair
swear
their
bear
square
scare
welfare

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<td>country</td>
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**Block4**

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<td>greet</td>
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<td>hammer</td>
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<tr>
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</table>
APPENDIX G

BRAIN AREAS

Fig G.1: Brain areas: main gyri and sulci.
BIBLIOGRAPHY


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