ORBITOFRONTAL CORTEX LESIONS ATTENUATE AFFECTIVE BIASES

IN ECONOMIC DECISION-MAKING

By

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACC	anterior cingulate cortex
ACOM	anterior communicating artery
ANOVA	analysis-of-variance
BA	Brodmann area
BOLD	blood oxygen level-dependent
CT	computed tomography
DLPFC	dorsolateral prefrontal cortex
Fig.	figure
fMRI	functional magnetic resonance imaging
FOV	field of view
FSIQ	full scale intelligence quotient
MNI	Montreal Neurological Institute
MRI	magnetic resonance imaging
ms	millisecond
n.s.	not significant
OFC	orbitofrontal cortex
OMPFC	orbitomedial prefrontal cortex
PANAS-X	Positive and Negative Affect Schedule –Expanded Form
RT	reaction time
SD	standard deviation
SE	standard error
T	Tesla
TE	echo time
TR	repetition time
VLPFC	ventrolateral prefrontal cortex
VMPFC	ventromedial prefrontal cortex
VUIIS	Vanderbilt University Institute of Imaging Sciences
WAIS-III	Wechsler Adult Intelligence Scale – Third Edition
WASI	Wechsler Abbreviated Scale of Adult Intelligence
WMS-III	Wechsler Memory Scale – Third Edition

ABSTRACT

The orbitofrontal cortex has been speculated to play an important role in the processes that allow emotional factors to influence decision-making. In recent neuroimaging studies, orbitofrontal activity patterns have been linked to framing bias susceptibility in economic choice-behavior. However, it is still unclear whether orbitofrontal function directly contributes to the emergence of such observed framing bias. Hence, in the current study, we sought to examine the effect of orbitofrontal cortex (OFC) lesions on framing bias by investigating economic choice-behavior of twelve OFC lesion patients using a financial decision-making task. Results showed OFC lesion patients exhibit marked reduction in framing bias, which indicated OFC lesions disrupt processes that adapt choice-behavior to contrasting affective contexts. Furthermore, OFC lesion patients were no more likely than controls to choose the gamble option over the sure option and vice versa in the task overall, which suggested that their reduced framing bias was neither due to generalized disinhibition of risk-taking tendencies, nor a broad and nonspecific shift in choice-preference irrespective of framing manipulations. Critically, OFC lesion patients revealed deficits in adjusting their choices according to varying reward magnitude and distinct relative reward values. This study provides key evidence in support of the hypothesis that the orbitofrontal cortex serves a critical role in guiding economic decision-making by integrating salient information about the affective context of potential choices.

CHAPTER I

INTRODUCTION

"It is not to be forgotten that what we call rational grounds for our beliefs are often extremely irrational attempts to justify our instincts."

- Thomas H. Huxley from *Aphorisms and Reflections*

Framing bias in economic decision-making

Decision-making is heavily influenced by the emotional context in which the choices are presented. Cancer treatment options can be made less appealing to patients, as well as to expert physicians, when the anticipated treatment outcome is presented as mortality rate rather than survival rate. Individuals are more willing to accept a business contract under negotiation when the same offer is illustrated as gains rather than losses on their part. Even moral judgment on an ethical dilemma can be swayed by changing the word-order and phrasing that are used to describe the available courses of action (McNeil, Pauker, Sox, & Tversky, 1982; Neale & Bazerman, 1985; and Petrinovich & O'Neill, 1996). This psychological phenomenon, known as the *Framing effect,* has been repeatedly demonstrated through a wealth of empirical data generated from a diverse set of

experimental paradigms across various domains of human judgment that involves

decision-making (Kühberger, 1998).

Two psychologists, Kahneman and Tversky, recognized such deviation from

rational decision-making as both systematic and pervasive in normative economic choice-

behavior and further integrated this insight as a key tenet in their *Prospect Theory*

(Kahneman & Tversky, 1979; Tversky & Kahneman, 1981). As an alternative to the

Expected Utility Theory, which assumed individuals to be coolheaded, consistent, and logical

decision-makers, the *Prospect Theory* acknowledged the counter-utilitarian and

impressionable nature of the human mind and incorporated a behavioral model of

economic choices that more successfully illustrated economic decision-making in the real

world. A key piece of insight from this model was that individuals are more sensitive to

losses than gains, and therefore impose a skewed weighting of importance in their

economic choices by showing a greater degree of bias against choices perceived as losses

compared to those perceived as gains (Tversky & Kahneman, 1992; Novemsky &

Kahneman, 2005). Because attention paid to gains and losses is both inherent and salient

in economic decision-making, it is likely to be particularly susceptible to the influence of

framing biases.

Taking advantage of this knowledge, cognitive neuroscientists have been

employing economic decision-making tasks in neuroimaging studies to identify and

elucidate the neural mechanisms from which framing biases originate. Recent

neuroimaging studies have investigated the neural correlates of framing effect in human

subjects, results of which appear to suggest that regions of the orbitofrontal cortex (OFC)

are a key component contributing to the manifestation of framing biases. De Martino and

colleagues (2006) conducted an fMRI study using a binary forced-choice financial

decision-making task in healthy normal subjects to investigate the neural correlates

associated with changes in choice behavior when options with equal mathematical value

are framed as losses or gains (see task description in *Methods* section). Replicating common

behavioral results associated with *Prospect Theory* (Tversky & Kahneman, 1992; Kahneman

& Tversky, 1979), they found healthy normal individuals showed greater bias against

economic choices framed as losses compared to choices framed as gains. More

interestingly, the study also found a strong correlation between individual differences in

the degree of framing bias displayed in their behavioral choice-patterns and blood oxygen

level-dependent (BOLD) activation level in the orbitomedial prefrontal cortex (OMPFC).

In particular, individuals who showed greater susceptibility to framing bias in the task

exhibited diminished medial OFC activity (De Martino, Kumaran, Seymour, & Dolan,

2006).

Significance of OFC function in the emergence of framing bias

Admittedly, it is still unclear as to what exactly the observed negative correlation between OFC activation and the framing bias magnitude reported in the De Martino et al. (2006) study represents with regards to the neurocognitive mechanisms involved. Nevertheless, one could hypothesize that OFC's role in framing bias is directly related to evaluation of potential reward choices. This hypothesis implicates the preexisting knowledge about the OFC's function to the emergence of framing bias. From this perspective, activity patterns in the OFC should reflect its influence on specific processes associated with valuation of reward choices. Indeed, accumulating evidence from numerous studies within the most recent decade suggest the OFC's function in decision-making as encoding reward value associated with various types of reward choices in both humans (Plassmann, O'Doherty, & Rangel, 2007; FitzGerald, Seymour, & Dolan, 2009; Zald, 2009; Chib, Rangel, Shimojo, & O'Doherty, 2009; Kennerley, Behrens, & Wallis, 2011) and in nonhuman primates (Tremblay & Schultz, 1999; Padoa-Schioppa & Assad, 2008).

While OFC appears to be a key structure involved in value-coding of reward choices, it is worth noting that there are other regions in the brain besides the OFC that contribute to processing affective information related to economic decision-making. As is

the case with other complex behaviors, cognitive processes distributed throughout the

brain work in concert to give rise to economic choice behavior. For instance, the

amygdala and the anterior cingulate cortex (ACC) are two amongst several regions

known to have significant affective processing functions. The amygdala, as already noted

earlier, is thought to bias decision-making by detecting emotional salience of stimuli

(Bechara, Damasio, Damasio, & Lee, 1999). The ACC, especially the dorsal portion, has

been found to be responsive to outcomes considered aversive or signaling reductions in

reward (Bush, Vogt, & Holmes, 2002). Moreover, prefrontal regions other than the OFC,

such as the dorsolateral prefrontal cortex (DLPFC), could contribute to decision-making

by modulating the manner in which affective information is processed in economic

decision-making. However, the OFC is known to have anatomical features fundamentally

distinct from this and other prefrontal regions, resulting in computational capacity

dissimilar from those regions (Zald, 2007). This suggests the possibility that the OFC

could provide functionally distinct contributions to economic decision-making by

mediating the reward valuation process of choice behavior (Padoa-Schioppa, & Assad,

2006, Wallis, 2007; Plassmann et al., 2007).

OFC's affective processing function influences evaluation of reward choices

Reliable prediction and evaluation of reward value is important in decision-making (Schultz & Dickinson, 2000). By the same token, without a reliable and context appropriate evaluation of different reward signals, economic decision-making processes can become very inconsistent (let alone rational). Because the availability of potential reward options frequently changes in the real world, encoding the relative reward value associated with the potential options allows for an efficient and flexible comparison of choices. OFC appears to be contributing to the evaluation of reward in this regard. For instance, monkey single-cell recording studies have shown increased activity in the OFC in response to expectation of the preferred reward between two options being compared. This is true regardless of the physical reward properties, (Tremblay & Schultz, 1999) as well as for relative preference of both rewarding and aversive outcomes (Hosokawa, Kato, Inoue, & Mikami, 2007).

Furthermore, the OFC seems to be critical for processes that adjust the value assigned to available choices based on changing motivational significance of specific stimuli. Non-human primate studies show monkeys with OFC lesion continue to select foods that their healthy counterparts would have given up after becoming selectively

satiated (Izquierdo, Suda, & Murray, 2004). Comparably, in a human neuroimaging

study, participants who were fed to satiety on one type of food showed selective decrease

in caudal OFC region's BOLD signal in response to the specific stimuli of the satiated

food. This signal decrease was coupled with subjective reduction in desirability of the

satiated food (Kringelbach, O'Doherty, Rolls, & Andrews, 2003). Non-human primate

lesion studies also appear to confirm the OFC's key role in determining behavioral

responses to reward-related decision-making. For example, an excitotoxic lesion to a

monkey OFC causes impairment in suppressing previously learned stimulus-reward

association (Dias, Robbins, & Roberts, 1996).

Taken together, the OFC's activity appears to be sensitive to shifting motivational

values assigned to various rewards and reward predicting signals, depending on the

desirability and the availability of different alternatives. Much research has been done to

elucidate the OFC's functions in regards to its processing capacity relevant to economic

decision-making, results of which suggest its important contribution to subjective

valuation of reward. These findings suggest that the OFC is a key component for

promoting choice-behavior adjustments in response to altered contingencies between the

reward and reward predicting stimuli. Correlational evidence, however, from human

neuroimaging studies investigating the neural correlates of framing bias may not be

sufficient to propose a causal link between the OFC and its hypothesized function in promoting the emergence of framing biases. Also, given available non-human primate lesion data, it is not unreasonable to suspect that the OFC may causally influence affective and motivational aspects of economic decision-making such as framing biases associated with monetary loss and gain.

Current Study

Here, we investigate to what extent OFC lesions in human subjects influence the normative patterns of economic decision-making, where choice-preference are flexibly adjusted according to the affective context in which available monetary reward option are presented. More specifically, we examined (i) whether OFC lesions undermine the normal process of reward-choice evaluation by disrupting processes that bias choice-preference in contrasting affective context (i.e., monetary reward choices framed as losses or gains) and (ii) whether the putative deviation from normative choice-patterns in OFC lesion patients reflect generalized disinhibition of risk-taking tendencies and a broad shift in choice-preference; or more specific alteration associated with sensitivity to reward magnitudes. To addresses these questions, we used an economic decision-making task previously used in the De Martino et al. (2007) study.

In accordance with prior studies that suggest OFC activity codes for subjective

value of reward choices (Trembley & Schultz, 1999; Tom, Fox, Trepel, & Poldrack, 2007)

we predicted that OFC lesions patients would show less change in response to different

affective contexts in which the monetary reward choices are presented. Specifically, we

predicted that OFC lesion patients would show smaller magnitude of framing bias such

that they would exhibit a lesser degree of choice-preference change in response to being

presented with choices framed as losses versus gains. It was also predicted that lesion

patients would show reduced sensitivity to varying reward magnitude compared to

demographically matched controls.

CHAPTER II

METHODS

Participants

OFC lesion patients

Twelve patients with OFC lesion were included in the study. They were recruited

through the Vanderbilt University Medical Center Neurosurgery and Radiology Clinics.

The Medical Center electronic data repository, Star-Panel, was used to identify OFC

patients eligible for participation in the study. Star-Panel's Neurosurgery and Radiology

clinic databases were queried using OFC-related keywords: e.g., "orbitofrontal"; "inferior

frontal"; "subfrontal"; "gyrus rectus"; "anterior communicating artery". Relevant

medical records of identified patients were reviewed to determine their eligibility, and

eligible individuals were contacted in writing, to which they could respond their interest

in study participation. All patients had a brain lesion affecting the orbitofrontal cortex

(i.e., ventral surface of the prefrontal cortex that include gyrus rectus; medial orbital

gyrus; anterior and posterior orbital gyri; and lateral orbital gyrus). The site of the lesion

was ascertained by acquiring a brain MRI or CT scan in addition to radiologists' or

neurosurgeons' reports. Exclusion criteria included damage outside the orbitofrontal cortex, alcohol or drug dependence, and a full-scale intelligence quotient (FSIQ) below a cut-off of 75 (1 standard deviation below the mean) in the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III). Five of the patients were male and 7 were female, and their ages ranged from 26 to 56 years (mean = 42.6 years, SD =10.9 years). The time between surgery and their taking part in the study ranged from 1 to 12 years. Three had suffered from ruptured anterior communicating artery aneurysm which was clipped, 2 had suffered from focal head injury, and 7 other patients had undergone resection of portions of the OFC due to the following: 3 from meningioma, 2 from intractable focal epilepsy, 1 from cavernous angioma, and 1 from neurofibroma. The study protocol was approved by the Vanderbilt University Institutional Review Board. A complete description of the study was provided to all participants, and all subjects provided written informed consent.

Healthy controls

Twelve demographically matched healthy controls were recruited through advertisements posted on local craigslist webpage, a high-traffic online community featuring advertisements and forums. Each control subject was specifically recruited to match, within a pre-defined margin of difference, the demographics of the OFC lesion

patient that they were matched to. Specifically, matched-controls were no more than 3

years younger or older; and within 2 years of difference in formal education level

compared to the patient subject they were matched to. Controls were also matched for

sex. Exclusion criteria included past history of head injury, drug and alcohol dependence,

current use of psychoactive medications, past or current diagnoses of major psychiatric

disorders, and a full-scale intelligence quotient (FSIQ) below a cut-off of 75 (1 standard

deviation below the mean) as measured by the Wechsler Abbreviated Scale of Intelligence

(WASI). Healthy controls were well matched to OFC lesion patient participants' age

(matched-pairs t_{11} = - 1.0, p = n.s.), sex (all identical to matched patient), education level

(matched-pairs t_{11} = 0.65, p = n.s.), full scale IQ (matched-pairs t_{11} = 1.16, p = n.s.) and

general memory (matched-pairs t_{11} = 1.62, p = n.s.) from the Wechsler Memory Scale –

Third Edition (WMS-III).

Questionnaire: State affect

Additionally, state (cf., as opposed to trait) measure of mood was assessed using a

24-item version of the Positive and Negative Affect Schedule – Expanded Form (PANAS-

X; Watson & Clark, 1999). The PANAS-X, a well-validated self-report measure of mood,

was administered to all subjects on the day of testing prior to completing the economic

decision-making task. Questions in the PANAS-X was comprised of 24 affectively

valenced words that subjects indicate the "extent to which they feel this way, right now"

using a Likert scale from 1 (indicating "Not at all") to 7 (indicating "Extremely"). For the

present study, we used the total positive affectivity (PANAS-PA) and negative affectivity

(PANAS-NA) scores (defined in Watson & Clark, 1999). There was no between-group

difference in either the positive affect scores (matched-pairs t_{11} = -0.90, p = n.s.) or in the

negative affect scores (matched-pairs t_{11} = -1.18, p = n.s.). A summary of demographics

and neuropsychological testing data is shown in Table 1.

Table 1. Means, standard deviations and group comparison of demographic data, IQ, memory, and affect scores

Variable	OFC lesion			Healthy controls		
	N	*Mean*	*SD*	N	*Mean*	*SD*
Age	12	42.6	10.9	12	42.1	11.2
Male/Female	12	5/7		12	5/7	
Education (years)	12	15	2.7	12	14.7	3.2
Full Scale IQ (WAIS-III or WASI) [†]	12	110 [*]	13	12	116	10
General Memory (WMS-III)	12	108	13	12	117	16
PANAS-PA	12	45.8	2.9	12	43.0	10.6
PANAS-NA	12	27.7	3.9	12	25.2	5.3

[*] One OFC patient's FSIQ was estimated from Performance IQ (PIQ) due to incomplete test data.

[†] WAIS-III was administered to OFC lesion patients and WASI was administered to healthy controls.

Verification of Lesion Location using Structural MRI

For each OFC lesion patient, structural brain MRI scans were completed on a 3T

Philips Intera Achieva scanner (The Netherlands) at the Vanderbilt University Institute of

Imaging Sciences (VUIIS). High- resolution T1-weighted structural images (TR = 8.969

ms; TE = 4.6 ms; in-plane resolution = 1 mm^2; FOV=24x24cm2; matrix size=256x256;

slice thickness = 1 mm; no gap) were acquired and used to ascertain the presence,

location, and extent of the OFC lesion in each patient subject. Individual MRI scans were

carefully screened to ensure that no lesion was present outside the OFC region. One

subject was excluded from the study due to additional lesion in the parietal lobe. The T1-

weighted structural images for two participants were acquired on a 1.5 T Philips scanner

(in-plane resolution = 1 mm^2; slice thickness = 1.2 mm) due to contra-indications for

higher field scanning. The common regions of OFC lesions were determined by creating

an overlay images using the MRIcron image analysis program

(http://www.cabiatl.com/mricro/mricron/; Rorden, Karnarh, & Bonilha, 2007).

Patients with an OFC lesion due to a ruptured ACOM aneurysm – all of whom had

lesions in the posterior portion of the gyrus rectus, right greater than left – were not

included in the overlay image, due to technical difficulties creating an individual lesion

maps (i.e., The nature of their lesion was vascular in origin, hence lesion-mapping

method used for surgical resections and focal damage cases did not work on structural

images with ACOM aneurysm). Lesions were overlaid on an MNI template brain map

provided by the MRIcron program. The most common overlap was found in the medial

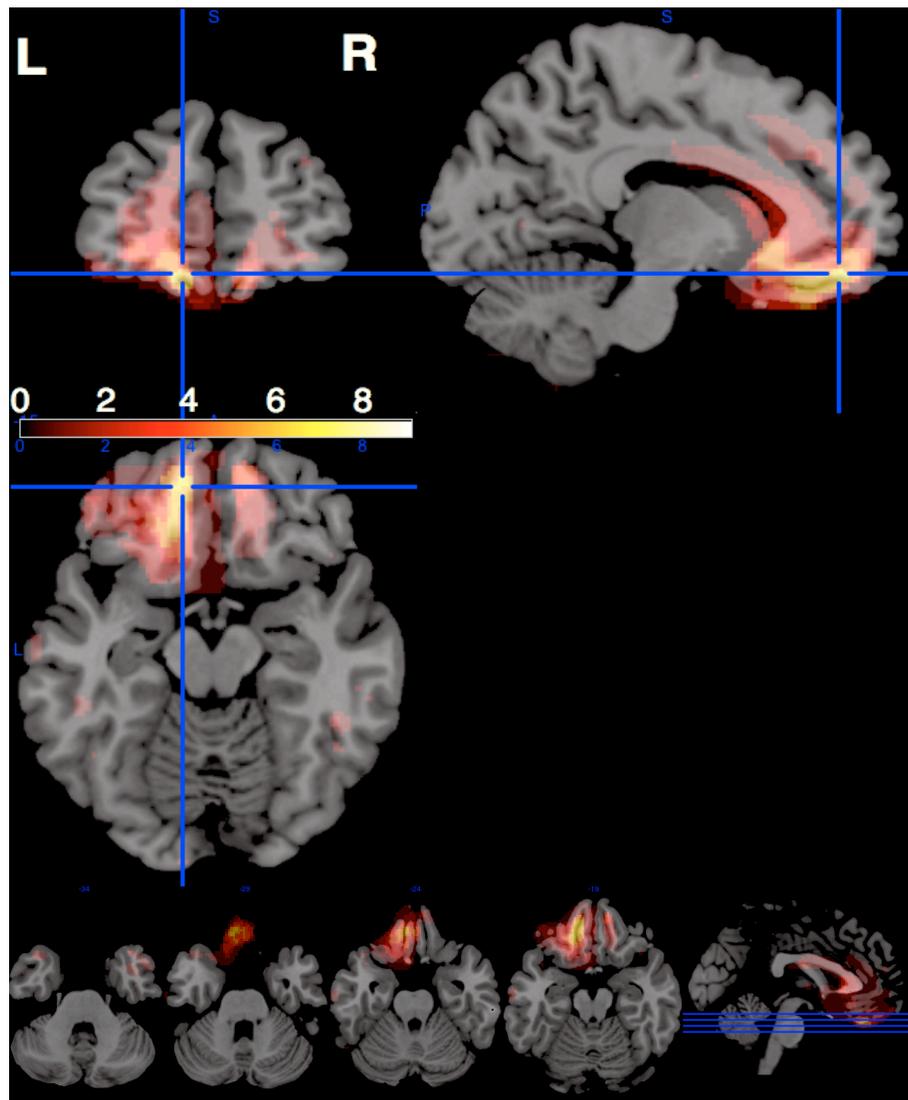orbital gyrus, left greater than right (MNI coordinates x = - 12, y = 49, z = - 15, Fig. 1).

Figure 1. Overlap of lesions in OFC lesion patients (n=9), excluding ACOM aneurysm
cases. Heat-map indicates the density of lesion-overlap (i.e., number of patients showing
lesion to the colored area).

Behavioral Measure: Framing Task

Task Design

A computerized financial decision-making task adapted from De Martino et al.

(2006) was used to assess the effect of OFC lesions on normative framing biases associated

with economic choices (Fig. 2). In this task, subjects received a cue indicating the amount

of money that they would initially receive in that trial, after which they had to choose

between a sure option and a gamble option presented in the context of two different

frames. In the beginning of each trial, a fixation cross was shown at the center of a

computer display for 2000 ms ("Start of trial", Fig. 2). Subjects were then presented with,

for 2000 ms, the amount of money they would initially receive in that trial: $50, $75, or

$100, randomized across trials ("Initial amount", Fig. 2). However, they were not

guaranteed to keep this initial amount received. Rather, in the subsequent screen

("Choose between the gamble or sure option", Fig. 2), subjects were asked to choose,

within a 2000 ms window, between the sure option (to keep a portion of the initial

amount with 100% certainty); and the gamble option (to gamble for a chance to keep the

entire initial amount given with a known probability of winning or losing). In case the

subject did not respond within the 2000 ms window, it was recorded as a no-response trial

and excluded from analysis. The proportion of trials with no response was minimal in the

16

OFC lesion group (mean % no response = 0.58%, SD = 0.51) as well as the control

group (mean % no response = 1.25%, SD = 1.29), and there was no difference in the

proportion for trials not responded (matched-pairs t_{11} = 1.61, p = n.s.). The sure option

was formulated as either the amount of money to "KEEP" from the initial starting

amount (e.g., "KEEP $20" of the $50, gain frame, Fig. 2A) or as the amount of money to

"LOSE" from the initial amount (e.g., "LOSE $30" of the $50; loss frame, Fig. 2B). The

proportion of initial amount offered in sure options was varied such that 20%, 40%, 60%,

or 80% of the initial amount was offered for both framing types. For example, in case $50

was given as the initial amount, monetary gain of $10 (20%), $20 (40%), $30 (60%), or

$40 (80%) appeared as the sure option. The gamble option was identical in both frames

and was represented as a pie-chart depicting the probability of winning (blue), or losing

(red). The probability of winning/losing depicted in a pie-chart was: 20/80, 40/60,

60/40, or 80/20. The expected value of the sure option and the gamble option within a

given trial were matched such that the monetary amount offered through the sure option

was equivalent to the mathematical product between the probability of winning in the

gamble option (as shown via a pie-chart) and the initial amount the subject would win. In

order to examine study subjects' choice-preference pattern and risk-taking under

uncertainty (i.e., unknown probability), trials where the pie-chart is not present (40% of

17

all trials) were also included in the task (Fig. 2C). Because the pie-charts conveyed to subjects the probability of winning if they were to choose the gamble option, missing pie-charts meant unknown risk of not winning any money on that trial (or unknown chance of winning the entire sum of money).

Catch-trials

In order to gauge the two groups' ability to make optimal choices based on numerical comparison of dissimilar expected monetary values, "catch-trials" were included in the task (De Martino et al., 2006). In this type of trial (20% of the all trials), the expected value of the sure and gamble option were markedly unbalanced. Two types of catch trials were used for each: *sure weighted* - where the sure option was 50% of the starting amount and the gamble option was a 5% probability of winning the starting amount; and *gamble weighted* - where the sure option was 50% of the starting amount and the gamble option was a 95% probability of winning the starting amount.

Task instruction and administration

Subjects were instructed to press the left arrow key (←) for the sure option and the right arrow key (→) for the gamble option as the sure option always appeared on the left side of the computer display and the gamble option always on the right. After task

instructions, all subjects completed a block of 8 practice trials while the experimenter

observed to ensure that subjected comprehended the task instructions given. All subjects

were administered 360 trials in total (144 trials with pie; 144 trials with no-pie, 72 catch-

trials), evenly divided into 6 blocks with 60 trials within each block.

On trials where subjects chose the gamble option, subjects were not given any

feedback about whether or not they won the gamble in individual trials. Instead, subjects

were given a chance to take a brief period of rest after completing each block, during

which they were presented with the total amount they have accumulated so far in the

task, which included earnings from both the sure option as well as the gamble option.

Subjects were informed that they would receive a sum proportional to their total winnings

at the end of the experiment (up to $ 20).

For analyses using between-subjects paired t-tests, each control subject was yoked

to one specific OFC lesion patient subject that they were matched to in terms of
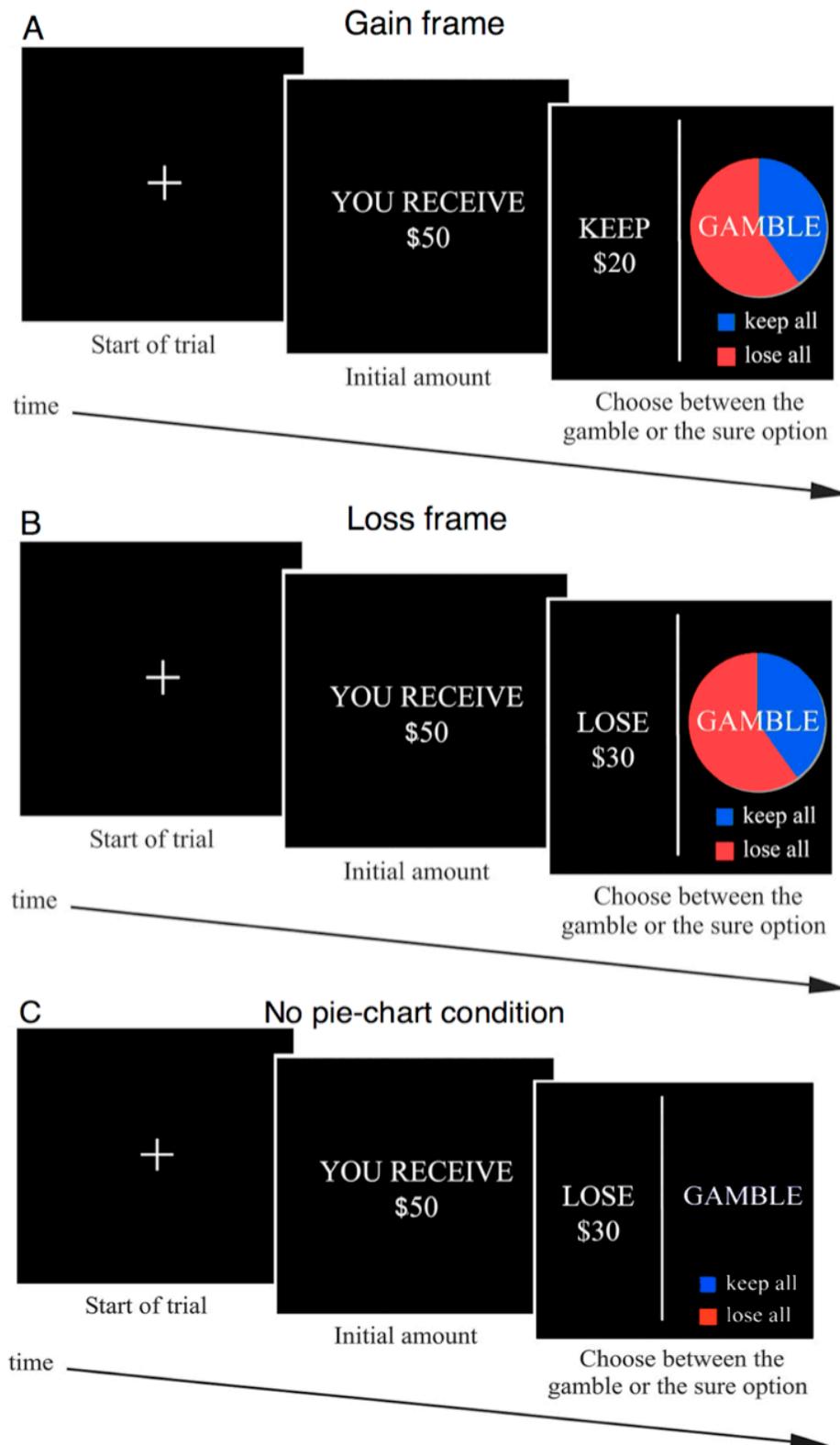
demographic variables.

Figure 2. The financial decision-making task

Choice-preference slope analysis

Each subject's sensitivity to varying relative reward magnitude was quantified by examining the slope of choice-preference change relative to four different proportions offered for the sure option. For the sure option of a given trial, subjects were offered 20%, 40%, 60%, or 80% of the initially received amount, from which they could choose to accept this sure option, or alternatively choose to gamble for a chance to keep the entire amount. For all subjects, proportion of trials chosen to gamble was plotted on a two-dimensional space for each of the four different relative monetary values (20%, 40%, 60%, and 80%), by assigning to each point an arbitrary x-axis coordinate that is equidistant from their adjacent proportion(s) (specifically, 20%: x = - 1.5, 40%: x = - 0.5, 60%: x = 0.5, 80%: x = 1.5). For each subject, a simple linear regression line slope was derived from these four points on a plane (i.e., coefficient b in the formula y = b x). Linear slopes for gain and loss framed trials were calculated separately.

CHAPTER III

RESULTS

Framing Task Results

Catch-trials

In catch-trials where the expected value of the sure and the gamble option was

markedly unbalanced, each group as a whole made their decisions in directions consistent

with the unequal weighting of the sure and the gamble options, albeit with some

variability observed within each group (Fig. 3). A repeated-measures analysis of variance

(ANOVA) revealed that there was no main effect of Group ($F_{1,22}$ = .20, p = n.s.) or Group

by Weighting-type (i.e., sure- or gamble-weighted; $F_{1,22}$ = .05, p = n.s.) interaction. This

suggested that the two groups were statistically no different in making optimal choices in

these trials. Moreover, there was a main effect of Weighting-type, such that subjects

showed preference for the gamble option in the gamble-weighted trials compare to sure-

weighted trials ($F_{1,22}$ = 60.69, p < 0.0001). Additionally, Further analyses of choice-

preference within each weighting-type using one-tailed null-hypotheses (probability of

subjects choosing the gamble option in gamble-weighted trials ≤ 0.5 ; probability of

subjects choosing the gamble option in sure-weighted trials ≥ 0.5) revealed that controls, irrespective of framing-type, preferred the gamble option in the gamble-weighted trials (gain-frame: $t_{11} = 2.16$, $p = 0.0267$; loss-frame: $t_{11} = 2.79$, $p = 0.0088$), and preferred the sure option in sure-weighted trials (gain-frame: $t_{11} = -13.70$, $p < 0.0001$; loss-frame: $t_{11} = -12.22$, $p < 0.0001$). Similarly, OFC lesion patients, irrespective of framing-type, preferred the gamble option in the gamble-weighted trials (gain-frame: $t_{11} = 1.85$, $p = 0.0459$; loss-frame: $t_{11} = 1.96$, $p = 0.0379$), and preferred the sure option in sure-weighted trials (gain-frame: $t_{11} = -5.01$, $p < 0.0004$; loss-frame: $t_{11} = -4.06$, $p < 0.0019$). This provided evidence that OFC lesion patients were able to make optimal decisions based on numerical comparison of expected value associated with potential choices.
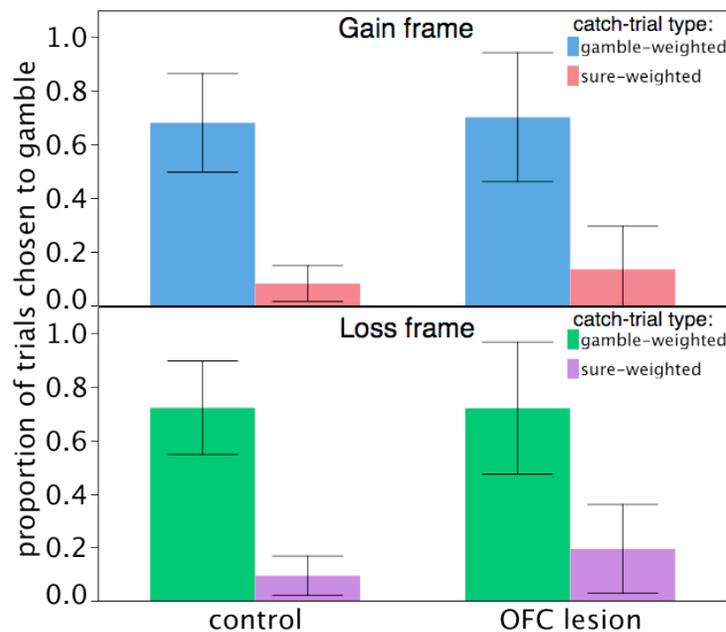

Figure 3. Subject performance on catch-trials

Choice-preference: percent gamble in trials overall

Patients with OFC lesions were no more likely than controls to choose the gamble option in trials overall (Fig. 4). On average, OFC lesion patients chose the gamble option in 43.6% (SD = 20) of all trials, and controls chose the gamble option in 42.9% of all trials (SD = 14). A matched-pairs t-test revealed that there was no group difference in proportion of trials chosen to gamble in trials overall (matched-pairs t_{11} = - 0.09, p = n.s.). Furthermore, overall choice preference for the gamble option or the sure option was statistically no different from chance (= 0.5) in either of the two groups (OFC lesion group: t_{11} = - 0.69, p = n.s.; control group: t_{11} = -1.69, p = n.s.). This indicated that the subjects displayed neither risk-seeking nor risk-aversion bias in their choice-preference.
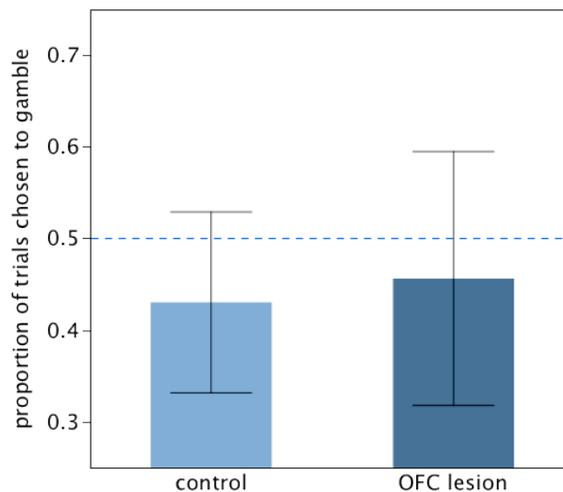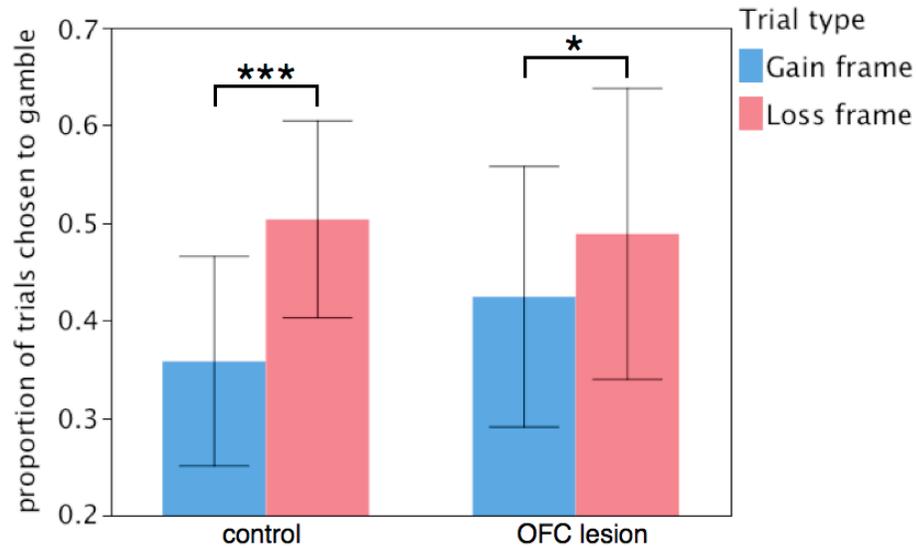

(Each error bar is constructed using a 95% confidence interval of the mean. Blue dotted line denotes the hypothetical point of complete ambivalence between two options)

Figure 4. Mean proportion of trials chosen to gamble in trials overall

Choice preference: percent gamble in each framing type

Patients with OFC lesion as well as healthy controls were both more likely to choose the gamble option when the sure option was framed as losses than when it was framed as gains (Fig. 5). A repeated-measures ANOVA with Group as a between-subjects factor showed that there was no between-subjects main effect of Group ($F_{1,22} = .27$, p = n.s.). However, there was a significant within-subjects main effect of Framing-type (gain vs. loss) such that proportion of trials subject chose to gamble in the loss frame was greater than that in the gain frame ($F_{1,22} = 29.26$, p < 0.0001). Additionally, a significant Framing-type by Group interaction was found ($F_{1,22} = 4.9137$, p = 0.0373), which indicated that the degree of increase in proportion gambled in the loss frame relative to the gain frame was dependent on the group, where the control group showed greater increase than the OFC lesion patient group.

Within the OFC lesion group, mean percentage of trials chosen to gamble was 42.4% (SD = 21) of the gain frame trials, and this increased to 48.9% (SD = 23) in the loss frame trials (mean difference of 6.5%; matched-pairs $t_{11} = 2.5$, p = 0.0297). Likewise within the control group, mean percentage of choices for the gamble option was 35.8% (SD = 17) in the gain frame, whereas this increased to 50.4% (SD = 16) in the loss frame trials (mean difference of 14.6%; matched-pairs $t_{11} = 4.68$, p = 0.0007).
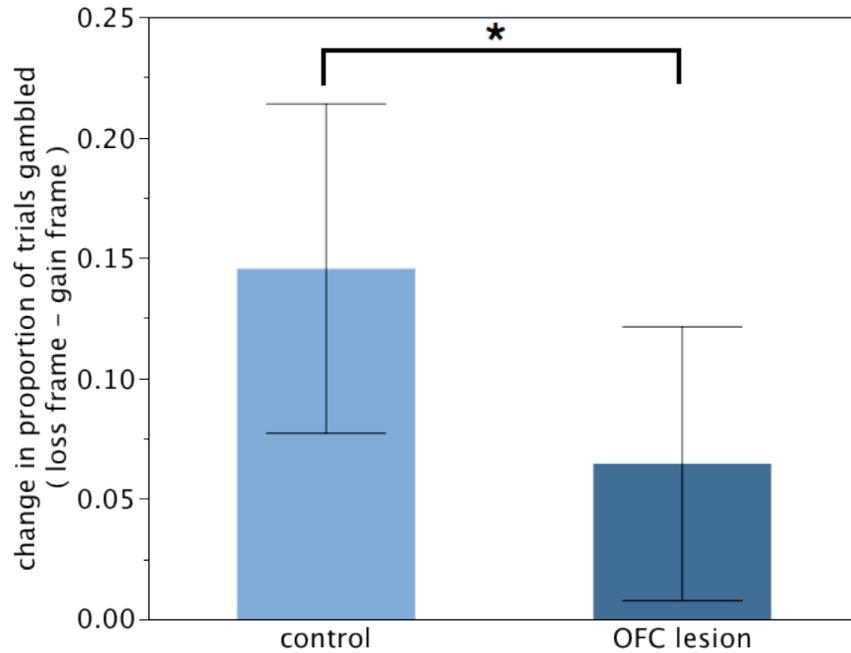
matched-pairs t-tests: * p < 0.05, ** p < 0.01, *** p < 0.001

(Each error bar is constructed using a 95% confidence interval of the mean.)

Figure 5. Proportion of trials chosen to gamble under different frames

Shifting choice-preference: magnitude of framing bias

The magnitude of the OFC lesion group's framing bias (mean = 6.5%, SD = 8.9) was significantly smaller (Fig. 6) than that of the control group's (mean = 14.6%, SD = 10.8): matched-pairs t_{11} = 2.45, p = 0.0321. The magnitude of framing bias was estimated for each individual from the difference in proportion of trials chosen to gamble between the gain and loss frame conditions (i.e., magnitude of framing bias = % gamble loss frame - % gamble gain frame).

26

Figure 6A. Framing bias magnitude: group comparison (indexed from change in proportion of trials chosen to gamble; proportion gambled in loss frame – proportion gambled in gain frame)
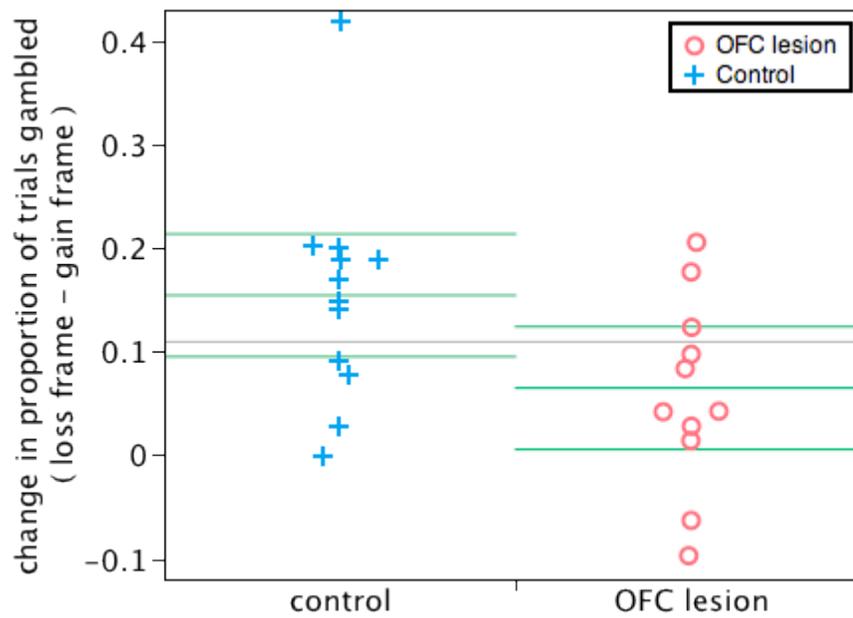

middle green line in each group represents the mean;

upper and bottom lines are constructed using 95% confidence interval of the mean

Figure 6B. Framing bias magnitude: individually plotted

OFC lesion patients' choice pattern in response to varying proportions of initial amount offered for the sure option indicated their diminished behavioral sensitivity to variations in monetary value (Fig. 7). Comparison of linear slopes derived from choice patterns in varying reward magnitudes (see *Methods* for mathematical derivation used) indicated that controls exhibited a robust decrease in preference for the gamble option as the proportion offered from the initial amount increased in the sure option, and these negative slopes were significantly different from zero (gain frame: mean slope = -17.7, SD = 12, t_{11} = - 5.05, p = 0.0004; loss frame: mean slope = -15.4, SD = 14, t_{11} = - 3.89, p = 0.0025). In contrast, the OFC lesion group's linear slope was not significantly different from zero in either of the two framing conditions (gain frame: mean slope = -0.04, SD = 22, t_{11} = - 0.70, p = n.s.; loss frame: mean slope = -0.004, SD = 21, t_{11} = - 0.07, p = n.s.).
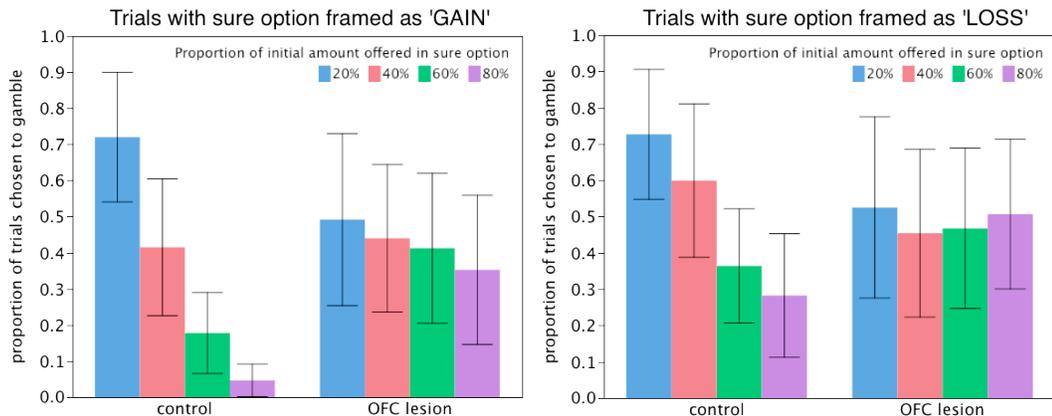
(Each error bar is constructed using a 95% confidence interval of the mean.)

Figure 7. Proportion of trials gambled for sure options varied in % of initial amount

28

Additionally, the OFC lesion group's slope was significantly less steep compared to the control group's slope. Levene's test for unequal variances revealed unequal variances between the two groups (gain frame: $F_{1,12} = 7.84$, p = 0.0104; loss frame: $F_{1,12} = 3.46$, p = 0.0764), therefore, a direct group comparison of the slopes were completed using the Welch's t-test that assumes unequal variances between groups. Based on the a priori prediction that the OFC lesion patient groups' reward magnitude sensitivity would be reduced compared to controls (i.e., slope would be less steep than that of healthy controls), using one-tailed tests was justified. As predicted, the OFC lesion group's slope was less steep in both the gain frame (Welch's $t_{17.1} = 1.83$, 1-tailed p = 0.0426) as well as the loss frame (Welch's $t_{18.8} = 2.05$, 1-tailed p = 0.0274).

Sensitivity to relative monetary values

OFC lesion patients displayed blunted sensitivity to differences in the relative value of monetary offers. Across a subset of trials in the task, the relative monetary value of the sure option was varied while the absolute monetary amount offered as earnings for the sure option was held constant. For example, a trial offering $20 from the initial amount of $100 as the sure option and another trial offering $20 from the initial amount of $50 as the sure option in principle offered the same amount of money. However, the two sure options each represented monetary offers of distinct relative value. In the former,

29

only 20% of the initial amount was offered, while in the latter, 40% of the initially

presented amount was being offered. In order to examine the effect of differences in

relative monetary value on choice-preference, trials with identical dollar amount offered

as the sure option were further segregated depending on how much proportional value

the amount represented relative to the initial amount presented to the subject. This

resulted in four pairs of possible comparison, each of which offered two distinct relative

monetary values but of identical absolute monetary amount: $20 offered (20% of $100;

and 40% of $50), $30 offered (40% of $75; and 60% of $50), $40 offered (40% of $100;

and 80% of $50), and $60 offered (60% of $100; and 80% of $75). For each one of these

four pairs, a matched-pairs test was performed to detect the presence of choice-preference

bias against the sure option offering lesser relative monetary value. One-tailed tests were

used for these tests, since the sure options associated with greater proportional value were

expected to be more desirable than those with lesser proportional value.

Across all four monetary amounts, controls were consistently more likely to choose

against the sure option that has lesser value relative to the initial amount presented (Fig.

8): $20 (matched-pairs t_{11} = - 3.01, one-tailed p = 0.0060); $30 (matched-pairs t_{11} = - 1.94,

one-tailed p = 0.0390); $40 (matched-pairs t_{11} = - 2.99, one-tailed p = 0.0062); and $60

(matched-pairs t_{11} = - 2.26, one-tailed p = 0.0226). However, OFC lesion patients' choice

patterns indicated that they did not discriminate between distinct relative values

associated with sure options: \$20 (matched-pairs $t_{11} = -1.14$, one-tailed p = n.s.); \$30

(matched-pairs $t_{11} = 0.06$, one-tailed p = n.s.); \$40 (matched-pairs $t_{11} = 0.14$, one-tailed p

= n.s.); and \$60 (matched-pairs $t_{11} = 0.56$, one-tailed p = n.s.).
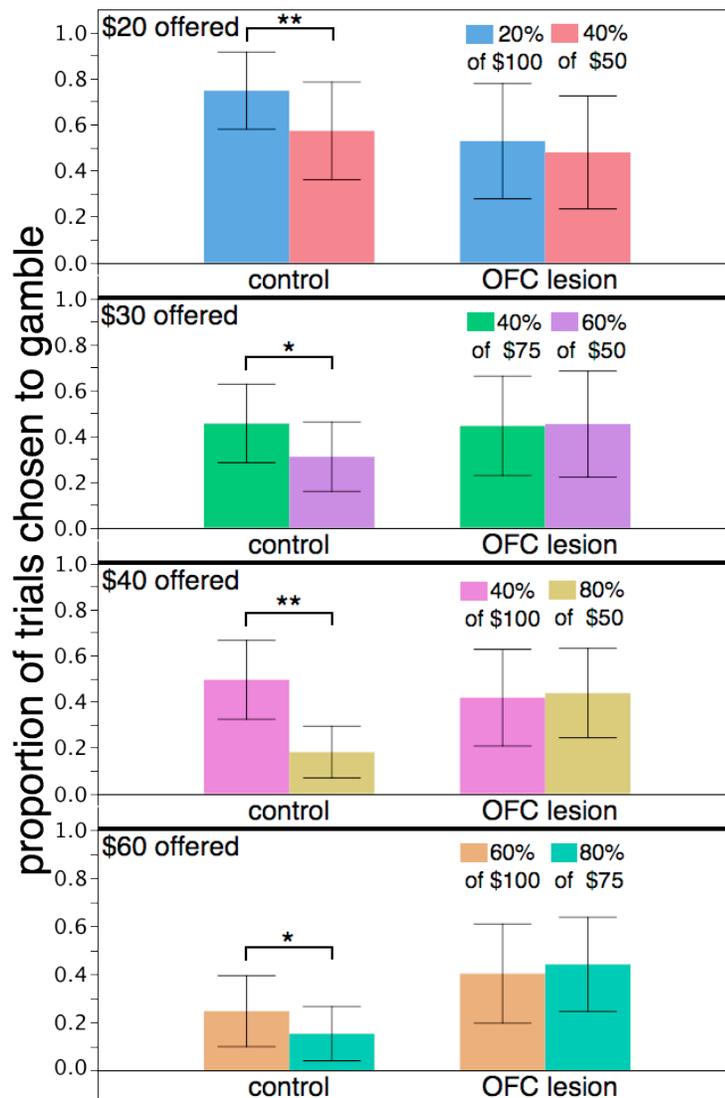
*p < 0.05, **p < 0.01; Each error bar is constructed using a 95% confidence interval of the mean.

Figure 8. Comparison of proportion-gambled when sure options across trials offered
different relative value (relative to initial amount shown) but identical absolute amount

Comparison of trials presented with and without a pie-chart for the gamble option

indicated that in both groups, absence of a pie-chart (as compared to the presence of it)

enhanced differentiation of choice-preference in regards to the variation in relative (i.e.,

proportional) monetary values of the sure option. A repeated-measures ANOVA, with

Group as a between-subjects factor; Pie-chart-presence as a within-subjects factor; and

linear slope derived from proportion gambled in response to variation in reward

magnitude as a dependent measure was conducted for each frame-type. In the gain

frame, there was no between-subjects main effect of Group ($F_{1,22}$ = 3.58, p = n.s.), or

Group by Pie-chart-presence interaction ($F_{1,22}$ = 0.21, p = n.s.). However, a main effect of

Pie-chart-presence was observed such that subjects were more sensitive to reward

magnitude change in trials where the gamble option did not provide information about

the probability of winning ($F_{1,22}$ = 20.58, p = 0.0002). Results were similar in the loss

frame. There was no between-subjects main effect of Group ($F_{1,22}$ = 2.41, p = n.s.), or

Group by Pie-chart-presence interaction ($F_{1,22}$ = 2.37, p = n.s.). But a main effect of Pie-

chart-presence was observed such that subjects were more sensitive to reward magnitude

change in trials with no pie-chart present ($F_{1,22}$ = 19.20, p = 0.0002).

Further analyses indicated that, for each framing-types, steeper choice-preference

changes were observed in trials without a pie-chart compared to trials with a pie-chart

(Fig. 9) for both the OFC lesion group (gain frame: matched-pairs t_{11} = - 2.75, p =

0.0189, loss frame: matched-pairs t_{11} = -3.39, p = 0.006); and the control group (gain

frame: matched-pairs t_{11} = - 4.89, p = 0.0005, loss frame: matched-pairs t_{11} = -2.91 , p =

0.0143).

When the reward magnitude sensitivity (linear slopes) of OFC lesion patients and

controls were directly compared, the two groups were not different in their sensitivity to

reward magnitude change in no pie-chart trials, as evidenced by no group difference

between mean slope coefficients: gain frame (matched-pairs t_{11} = - 1.53, p = n.s.), loss

frame (matched-pairs t_{11} = - 1.30, p = n.s.). This result showed that OFC lesion patients'

choice-preference pattern in the no pie-chart trials were similar to that of healthy

controls, in contrast to their choice-behavior in trials presented with a pie-chart which

showed clear difference from controls (Fig. 10).
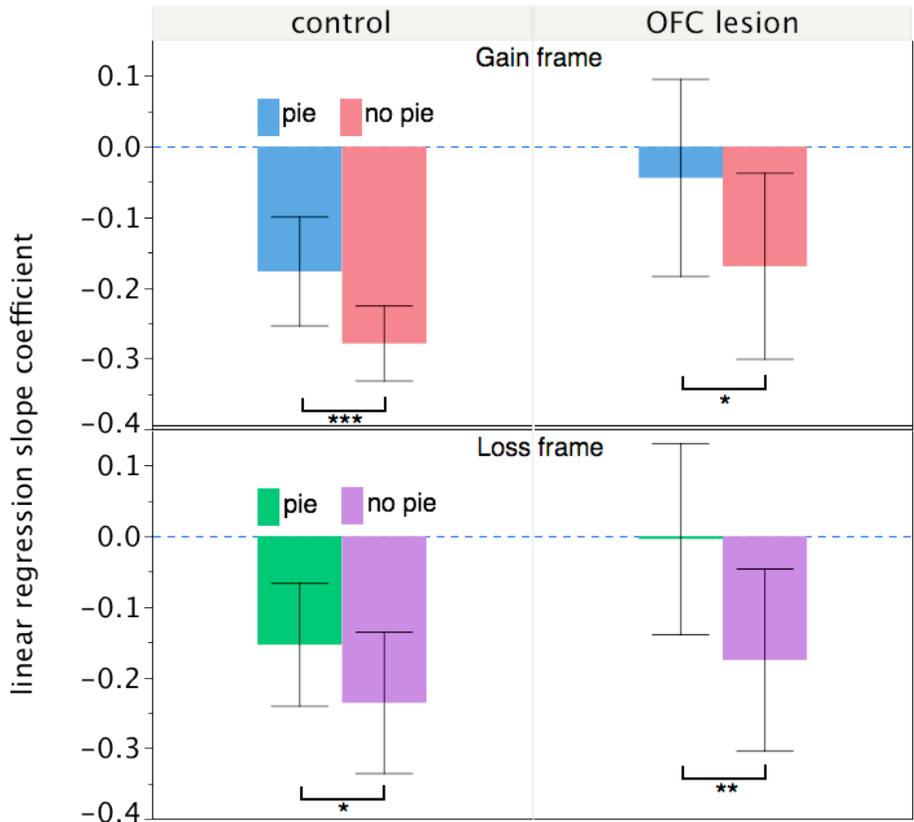
matched-pairs t-tests: p < 0.05, ** p < 0.01, *** p < 0.001

(Each error bar is constructed using a 95% confidence interval of the mean.)

Figure 9. Linear regression slopes in pie-chart present and pie-chart absent trials
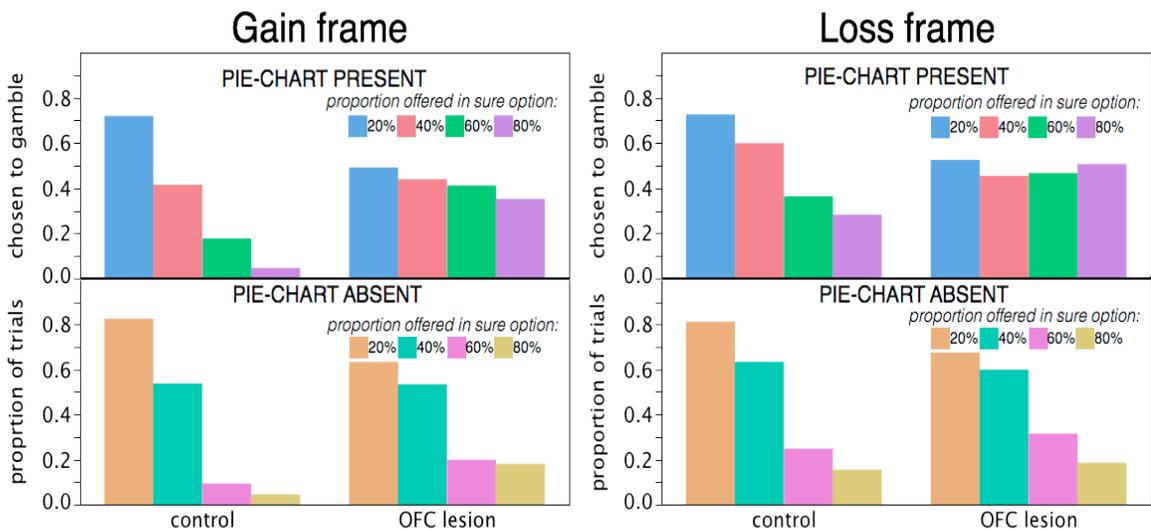

Figure 10. Choice-preference patterns in pie-chart present and pie-chart absent trials

Reaction time (RT)

A repeated-measures ANOVA showed that there was no main effect of group

($F_{1,22}$ = 1.04, p = n.s.). However, there was a significant main effect of frame (gain vs. loss)

such that time taken to reach a decision in the loss frame was significantly slower that that

in the gain frame ($F_{1,22}$ = 7.27, p = 0.0132). Additionally, a significant frame by group

interaction was found ($F_{1,22}$ = 5.12, p = 0.0339) which indicated that the degree of change

in reaction time was dependent on the group. Further analysis indicated that there was no

group difference in median reaction time for either of the two framing types (gain frame:

matched-pairs t_{11} = 0.73, p = n.s.; loss frame: matched-pairs t_{11} = 1.64, p = n.s.).

However, within-group analysis revealed that the control group subjects took significantly

more time to reach a decision in loss-framed trials (mean of median RT = 1613 ms, SD =

368 ms) than in gain-framed trials (mean of median RT = 1502 ms, SD = 350 ms) with a

difference of 111 ms (matched-pairs t_{11} = 3.69, p = 0.0036, see Fig. 11). This was not the

case for the OFC lesion group, as their performance indicated that there was no reaction

time difference (matched-pairs t_{11} = 0.29, p = n.s.) between the two framing types: gain

frame (mean of median RT = 1395 ms, SD = 400 ms); loss frame (mean of median RT =

1405 ms, SD = 429 ms).
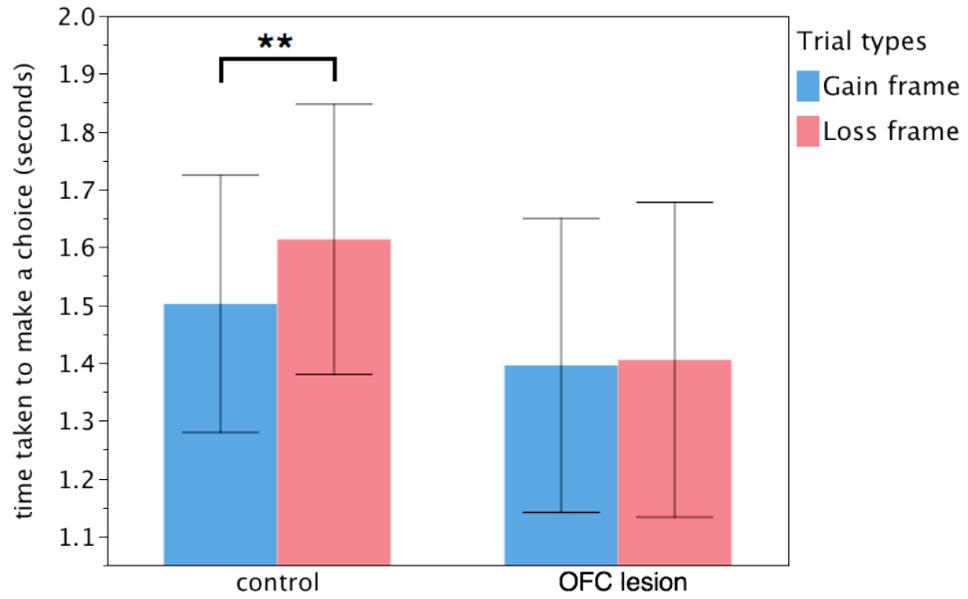
matched-pairs t-test: ** p < 0.01

Each error bar is constructed using a 95% confidence interval of the mean.

Figure 11. Time taken to choose between two options under different frame types

CHAPTER IV

DISCUSSION

The current study found that individuals with OFC lesions display attenuated

choice-preference adjustment to contrasting affective context. Specifically, it was shown

that OFC lesion patients' framing bias magnitude – as measured by the difference in

proportion of trials chosen to gamble between trials with financial choices framed as loss

versus gain – was smaller than that of healthy controls. OFC lesion patient subjects'

choice-patterns in catch-trials as well as no-pie chart trials indicated that they were able to

make the numerical comparison and appropriately weigh the value of two potential

choices. Nevertheless they showed marked reduction in sensitivity to the affective context

within which the potential monetary reward choices were embedded in (e.g., framing of

potential choices as gains versus losses; potential choices offering different proportion of

initial amount or different relative value). This is the first demonstration to our knowledge

of human subjects with OFC lesion exhibiting reduced framing bias in an economic

decision-making task. This extends previous work in human neuroimaging studies that

suggest possible involvement of the medial OFC region in contributing to the emergence

of framing biases (Deppe et al., 2005; De Martino et al., 2006; Tom et al., 2007).

De Martino et al. (2006)'s pioneering fMRI study using the same behavioral task as the current study found that higher OFC activity was associated with reduced framing bias, which can be speculated as evidence in support of the OFC as a neural substrate that contributes to reducing susceptibility to framing bias. Based on this notion, one would predict increased framing bias in individuals with OFC lesion. However, this was not the case in the present study. Rather, we found the exact opposite results, with OFC lesion patients showing more "rational" or "description-invariant" pattern of choice-behavior. While diminished influence of framing manipulations on choice-behavior may be considered more "rational" in the context of the decision-making task we used in the study, this pattern of choice-behavior may be far from adaptive decision-making in real life. It has been speculated that human emotion has been developed as a mechanism to more efficiently guide behavior (Damasio, 1994). In this sense, framing bias manifested by healthy normal subjects can be considered as a process that enables expedient adjustments of choice-behavior to meet the needs of the contexts within which decision-making takes place.

This notion of the OFC as a critical component in affectively guided decision-making is partially supported by evidence from a previous neuroimaging study that

demonstrated OFC's activation patterns share a remarkably similar trajectory with

behavioral pattern of choice-preference that reflect greater magnitude of subjective value

assigned to financial options framed as gains compared to those framed as losses (Tom, et

al., 2007). In their study, authors illustrated that patterns of "neural-loss-aversion"

(defined as difference between the slope of decreased regional brain activity in response to

increasing loss and the slope of increased regional brain activity in response to increasing

gain) was observed in ventromedial prefrontal cortex (VMPFC) activity such that greater

magnitude discrepancy in VMPFC BOLD signal change between increasing loss (which

resulted in VMPFC signal decrease) and increasing gain (which resulted in VMPFC

signal increase) was associated with greater degree of behavioral loss aversion. This

finding suggests that the ventro-medial region of the OFC activity patterns may

contribute to choices that individuals make under the perceived context of decision-

making. Findings from our study support this view and further suggest the general role of

the medial regions of the OFC as a neural substrate that guides choice-behavior by

integrating affectively relevant contextual information such as framing of financial choices

that suggests potential gains or losses and variation in the subjective and relative value of

monetary reward offered.

     Results from the current study additionally offer new insight into the original

findings reported by De Martino et al. (2006). In their study, authors reported that greater activity in the medial and central OFC regions were associated with decreased susceptibility to loss aversion related framing bias in economic decision-making. The authors speculated that, subjects with greater OFC activity associated with framing may have had more refined neural representation of their own emotional biases, thus allowing them to make their decisions more rationally. Based on this interpretation, we would have expected to see greater framing biases in lesion patients compared to controls. However, we found the opposite result of OFC lesion patients exhibiting attenuation of affective biases in decision-making. Our findings directly challenge the original interpretation by De Martino et al. (2006), and further suggest that functions of the OFC associated with representing affective significance of potential choices may subserve and promote the emergence of framing biases. It is possible that the correlation observed between framing susceptibility and OFC activity in the De Martino et al. (2006) study was due to asymmetric brain activity patterns elicited in response to choices framed as losses versus those framed as gains (Tom et al., 2007).

Importantly, OFC lesion patients did not manifest a general pattern of increased risk-seeking or risk-aversion in their choice-preference. This was reflected in their rate of choosing the gamble option in trials overall, which was comparable to that of controls.

This finding provides support for the idea that OFC damage may not necessarily lead to generalized disinhibition of risk-seeking. Our finding, however, must be understood from a context distinct from a previous report of left orbitofrontal lesion patients showing greater risk-seeking tendencies in a probabilistic gambling task (Floden, Alexander, Kubu, Katz, & Stuss, 2008). In contrast to the lack of trial-by-trial feedback in the economic decision-making task utilized in our study, the task used by Floden et al. (2008) provided specific feedback to subjects about the outcome of their choice in each trial, which could significantly alter the property of gambling behaviors in the task over time. Hence, their left OFC lesion patients' increased rate of choosing risky choices may reflect more of the patients' inability to appropriately incorporate task feedback to adjust their choices rather than a general mechanism of disinhibited risk-seeking.

The present study also found support for OFC as a neural substrate that enables adaptable choice-preference differentiation in value-based decision-making. Healthy controls showed a robust decline in their tendency to choose the gamble option when the alternative, the sure option, offered increasingly greater proportion of initially received amount. This clearly demonstrated that controls were able to differentiate their choice-preference in accordance with varying relative reward magnitude of the potential choice presented to them. However this was not the case with OFC lesion patients, as their

choice-preference patterns were essentially invariant across different proportions of

monetary reward offered, indicating their diminished sensitivity to using relative reward

magnitude information to guide their choice-behavior. OFC lesion patients also exhibited

diminished sensitivity to differences in the relative value of monetary reward. This was

apparent from comparing choice-patterns in trials with sure options of equal absolute

amount that are different in their relative value (when compared to the initial amount

offered). These results extend evidence from non-human primate single-cell recording

studies that show OFC's crucial function of coding for the relative preference of

rewarding (Tremblay & Schultz, 1999) as well as aversive outcomes (Hosokawa, Kato,

Inoue, & Mikami, 2007). In our study, financial choices framed as losses never truly

resulted in tangible monetary losses. However, when contrasted with other trials with the

sure option framed as gains, choices framed as losses were subjectively an aversive

outcome to subjects engaged in the task. Hence, our data may suggest that OFC lesions

lead to disruption not only in the processing the emotional significance of potentially

rewarding choices but also of potentially aversive ones.

The current study also found that when the reward value of the probabilistic

option (i.e., gamble option) is uncertain, patients and controls show greater sensitivity to

variation in values associated with the sure option. In other words, when subjects lacked

information about the probability of winning for the gamble option, (note that this effectively converts the gamble option to a psychologically ambiguous choice where individuals assume a 50/50 chance of winning), patients as well as controls showed greater degrees of differentiation among different relative reward values presented in the sure option. More importantly, OFC lesion patients' sensitivity to variation in reward values was not different from that of controls in these trials. In contrast, patient subjects were less sensitive to change in monetary reward magnitude variation compared to controls in trials with known probability of winning for the gamble option (i.e., trials with a pie-chart present). This showed that OFC lesion patients have an intact ability to process numerical value-related information, which further suggests that their diminished sensitivity to varied reward magnitude in the pie-chart present conditions do not reflect a general deficit in value comparison.

Our observation of control subjects showing increased reaction time in the loss-framed trials, as compared to the gain-frame trials is consistent with other studies that report similar findings of slower reaction time observed in negative compared with positive framings (Payne, Bettman, & Johnson, 1993 Gonzalez, Danda, Koshino, & Just, 2005). This may potentially reflect an extra step required to *avoid* the loss framed option and then consider the alternative option (gamble) than to just directly choose the certain

(gain). The finding of no difference in reaction time for the patient group demands further

clarification. However, our finding suggests that OFC lesion patients may not be

processing the gain and loss framed choices in a very different manner judging from the

reaction time data as well as our results showing significant attenuation in their framing

bias.

Our results raise further questions to be answered involving the specific affective

processing functions associated with sub-regions of the OFC. In the present study, the

common area of lesion was identified as the left medial OFC, near the medial orbital

gyrus and gyrus rectus. Interestingly, it has been demonstrated that lateral regions of the

OFC responds in a different manner compared to medial regions of the OFC. For

example, in an fMRI study where subjects were asked to consume highly palatable food

such as chocolate beyond satiety, the medial OFC activity showed commensurate

decreased after satiety, in keeping with the diminishing reward value of the chocolate they

were asked to consume, but activity in the lateral OFC increased showing the opposite

pattern to the medial OFC activity (Small, Zatorre, Dagher, Evans, & Jones-Gotman,

2001). This and other studies have suggested that while medial regions of the OFC serve

the function of coding for subjective reward values, the lateral portion of the OFC seems

to be more involved in suppressing or overriding previously acquired stimuli-reward

contingencies. (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001; Kringelbach, 2005). Observation of distinct activity patterns in the lateral OFC raises further questions about the involvement of other sub-regions of the OFC and the nearby frontal cortex region.

It is worth noting that the current study's OFC patients showed significant lesion overlap in the left hemisphere (see Figure 1). In the De Martino et al. (2006) study, OFC activity associated with individual differences in framing bias was found more in the right than the left. This particular finding of framing-bias-associated OFC activity being more lateralized to the right hemisphere was not explicitly addressed by the authors. However, another previous fMRI study using an economic decision-making task, not specifically related to framing bias, has reported similar patterns of right-sided OFC activity when subjects were exposed to financial outcome of gains versus losses (Kuhnen & Knutson, 2005). Assuming a greater role of the right OFC function in promoting framing bias, it is possible that potential OFC lesion patients with more right sided OFC lesion show greater attenuation of framing biases.

Moreover, correlational evidence from neuroimaging studies provide support for the involvement of posterior regions of the ventro-lateral prefrontal cortex (VLPFC, BA 47/12) in down-regulating amygdalar activity (Ray & Zald, in press). While amygdalar

activity was not a determinant of inter-subject variability in framing bias in the De

Martino et al. (2006) study, it did predict within-subject choices that are in accordance

with framing manipulations. Hence, it is possible to speculate that VLPFC exerts

inhibitory influence on framing biases. Future research addressing such questions about

the laterality of OFC's contribution to framing bias and clarifying possible involvement of

other frontal regions near the medial OFC can further augment the finding from the

current study.

The present study provides distinct contribution to our understanding of the

OFC's role in framing effect and value-based decision-making. The current study

additionally demonstrates how behavioral economics can be applied in lesion studies to

test hypotheses relevant to the functional significance of neural substrates being studied.

Moreover, in comparison to previous neuroimaging studies that provide correlational

evidence, the present study offers a more direct examination of the medial OFC's

contribution to affective biases involved in decision-making processes. Future lesion

studies could augment findings from the current study by further investigating the

involvement of other sub-regions of the OFC in context dependent and value-based

decision-making.

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