Universität Zürich[UZH] FORSCHUNGSKREDIT UZH

Fakultät:

Fakultät	***Wirtschaftswissenschaftliche Fakultät***
Gesuchstyp	*Postdoc*

1. Gesuchstellerin/Gesuchsteller:

Name	*Chumbley*
Vorname	*Justin*
Funktion	*Postdoc*
Akad. Grad	*PhD*
Geburtsdatum	*1977-02-23*
Nationalität	*Briton*

Privatadresse:

Strasse, Nr.	*Berninastr 8*
PLZ	*8057*
Ort	*Zurich*
E-Mail Adresse	*jrchum@gmail.com*
Telefon	*+41788678267*

Arbeitsadresse:

Fakultät	***Wirtschaftswissenschaftliche Fakultät***
Institut	*Dept Economics*
Strasse, Nr.	*Bluemlisalpestrasse 10*
PLZ	*8006*
Ort	*Zurich*
E-Mail Adresse	*jrchum@gmail.com*
Telefon	*+41788678267*

2. Projekt:

Das ist ein	*neues Gesuch*

Projekttitel:

Biological obstacles to the resolution of human social conflict? The role of Pavlovian versus Instrumental defensive responses.

Beginn	*2013-07-01*
Dauer in Monaten	*24*
Verlangter Betrag	*331602*

Zusammenfassung:

In order to survive and prosper, mammals must protect themselves and their access to resources such as territory and mates. To this end, evolution has furnished endocrine [1], visceral [2], immunological [3] and behavioural [2] defensive or 'stress' responses, and a capacity to tune these with experience[4]. Despite its importance to individual and social welfare, there is no clear standard for assessing if and when these hard-wired programs actually help us survive and prosper, particularly in the context of complex social environments. Despite anecdotal observations that our response to social conflict is often suboptimal and resembles evolutionarily

hardwired Pavlovian responses [5,6,7,8,9,10,11], this suboptimality and mechanism remain hypothetical. Yet it is crucial to know if there exist biologically programmed obstacles to conflict management. Such knowledge might also elucidate psychiatrically disturbed responses to social stressors such as conflict [5,6,7,8,9,10,11,12]: While biochemical paradigms have clearly demonstrated that runaway hormonal stress responses to conflict are disastrous to human health [13], a completely new paradigm is required to identify the existence and cost of runaway behavioural stress responses, and their relevance to psychiatry [5,6,7,8,9,10,11,12]. I hypothesize that, because Pavlovian behavioural stress responses are rigidly expressed according to hardwired program, they are often innappropriate and can paradoxically increase conflict and/or stress exposure, particularly in vulnerable individuals.

To quantify costly behavioural responses to social conflict, I will use novel experimental conflicts which have an optimal solution. I hypothesise that conflict is commonly mishandled in any situation where the best behavioural response contradicts a Pavlovian defensive reflex. In this proposal I will focus on just two aspects of human conflict in this underexploited field: defensive attack and defensive inhibition. Using fMRI I will examine the neurobiology of individual differences in these behavioural tendencies. This theoretically principled project will be the first to quantify the real social and personal costs of biologically hardwired defences.

In the setting of simple social interactions, I will first mathematically define the theoretically optimal defence strategy. This will provide a principled reference against which to define and quantify dysfunctional behaviours i.e. strategies which hurt more than they help. Focusing on non-clinical populations, the second aim is to examine if and when Pavlovian behavioural responses in particular can explain dysfunctional conflict, while rigorously excluding alternative hypotheses. This sets the foundation for future work identifying expression of these pathogenic mechanisms in clinically distressed versus healthy populations. There are three parts to the proposed project.

1. Developing realistic models of 'the behavioural stress response' requires us to combine and augment existing theories of defence: Homeostasis [1,3]/Fitness [14]/Expected-loss [15]/Nash-equilibria [15]/reinforcement-learning [16]/Free-energy [17]. I will initially model behavioural suboptimality by incorporating the impact of behavioural impulses on goal-directed social behaviour as prescribed by game theory [2,18,19,20].

2. Behavioural experiments: In two pilot studies I have already measured subjects' defensive behaviour in the context of real bilateral threats. These data on real social conflicts are the first of their kind and preliminarily suggest that Pavlovian behavioural responses do indeed derail conflicts. I will replicate/extend these results before analysing the underlying biology.

3. The biology of individual differences: Using fMRI I will also concurrently measure neuronal responses during defensive decision-making. I hypothesise that reactivity of subcortical systems (e.g. periaqueductal grey, central amygdala) explain between-individual differences in the expression of counterproductive defensive responses. I will correlate individual differences in this respect with hormonal and sympathetic stress responses (cortisol saliva and electrodermal), as well as questionnaire measures of trait anxiety disorders.

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3. Angaben zur Promotion:

Promotion	*2009-10-05*
Bezahlte Anstellung	*yes*
Lohnklasse	*18/01*
Seit	*2009-10-05*

Bemerkungen:

4. Finanzen:

A) Personalmittel:

Gesuchsteller

1.J. Anzahl Monate	*12*
1.J. Beschäftigungsgrad	*100*
1.J. Jahresbruttolohn	*0*
1.J. Anderer Jahresbruttolohn	*91327*
1.J. Effekt. Bruttolohn	*91327*
1.J. Arbeitsgeberbeitrag	*13699*
1.J. Total	***105026***

2.J. Anzahl Monate	*12*
2.J. Beschäftigungsgrad	*100*
2.J. Jahresbruttolohn	*0*
2.J. Anderer Jahresbruttolohn	*91327*
2.J. Effekt. Bruttolohn	*91327*
2.J. Arbeitsgeberbeitrag	*13699*
2.J. Total	***105026***

1. Mitarbeiter/in

Name	
Vorname	
Funktion	
Akad. Grad	
Geburtsdatum	*0000-00-00*
Geschlecht	*female*
Nationalität	
1.J. Anzahl Monate	*12*
1.J. Beschäftigungsgrad	*50*
1.J. Jahresbruttolohn	*84000*
1.J. Anderer Jahresbruttolohn	
1.J. Effekt. Bruttolohn	*42000*
1.J. Arbeitsgeberbeitrag	*6300*
1.J. Total	***48300***

2.J. Anzahl Monate	*12*
2.J. Beschäftigungsgrad	*50*
2.J. Jahresbruttolohn	*90000*
2.J. Anderer Jahresbruttolohn	
2.J. Effekt. Bruttolohn	*45000*
2.J. Arbeitsgeberbeitrag	*6750*
2.J. Total	***51750***

B) Protected Time:

Protected Time Total	

C) Sachmittel:

1. Material	*14500*
2. Verbrauchsmaterial	
3. Feldspesen und Reisen	*2000*
4. Verschiedenes	*5000*

Sachmittel Total *21500*

Total CHF ***331602***

D) Von anderer Seite verlangte Mittel:

Institution	
Entscheidungstermin	
Betrag	

Institution	
Entscheidungstermin	
Betrag	

Institution	
Entscheidungstermin	
Betrag	

Bemerkungen insgesamt:

Biological obstacles to the resolution of human social conflict? The role of Pavlovian versus Instrumental defensive responses.

The best response to any social conflict typically requires an intelligent strategy. We ask if evolutionarily hard-wired reflexes to social conflict can override that best response.

Justin Chumbley

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1. Research Plan

1.1. Statement of research

Background

Animals use many tactics to protect themselves, their wealth, territory and social-access from social and predator threats. While threats can influence almost every type of behaviour [1,2,3,4,5], specific defences include flight, freeze, threat, attack, signalling, submission, avoidance, withdrawal/retreat, orienting, vigilance/risk-assessment [6,7,8,9,10,11,12,13,14,15,16,17]. To be successful, the cost of any defensive response, or none, should be weighed against its benefits. Therefore an intelligent agent should select from, or augment, the above list depending on the unique challenges posed by a particular threat [18,19]. Such flexibility is particularly important in the face of intelligent opponents. In contrast, most biological theories of behavioural defence view opponents as unresponsive abstractions to which subjects respond [20,21,22,23,24], rather than as genuine participants in a behavioural interaction. This simplification is unrealistic for both interpersonal and predator threats[4]: modern-day social threats are typically embedded in complex, on-going conflicts.

We are therefore surprisingly ignorant about the biology and the real-world effectiveness of defensive decision-making [4]. Indeed animal defence strategies can be reliably counterproductive against real [25] and artificial [26,27] threats. Hard-wired Pavlovian systems have been implicated in these self-destructive phenomena by theory [28], ethology [29] and experiment[30]. These rapid reflexes can be self-defeating because they are triggered independently of the animal's goal i.e. even when punished. It has been repeatedly speculated that a Pavlovian mechanism underlies maladjusted social behaviour in humans, most evidently in hyper-defensive psychiatric disorders [8,9,31,32,33]. However, there is no *behavioural or causal evidence* for this theory in either healthy or clinical populations. In the next two paragraphs we will explore examples of social defence in animals: **defensive submission, defensive attack** and **defensive inhibition** ('freezing')**.**

Social threats can trigger ***defensive submission*** in social animals**.** Submission implies reduced competition for resources, reduced eye-contact [34], increased behavioural inhibition, escape/avoidance [35,36,37,38], submissive postures [22] and withdrawal. In principle, competent submission poses any goal-directed animal with a puzzle: balance the potential loss of resources against the potential costs from fighting. Instrumental submission should therefore be context-specific, taking into account relevant parameters (e.g. relative size/temperament/status of one's opponent [35,36,37,38]) and ignoring irrelevant ones. In contrast, theoretical models of behavioural evolution predict that submission [39,40,41,42,43,44] is rigidly governed by hardwired strategies that are only sensitive to some, evolutionarily important, parameters. Experimental evidence in animals confirms that simple reflexive strategies are indeed partly at play e.g. "cut-off" behaviours construed as Pavlovian responses [21,45]. The second example, **defensive attack**, is also rigidly expressed. Partly mediated by midbrain structures [46] defensive attack is sensitive to *proximity* of the opponent [24,47,48,49] but paradoxically insensitive to *threat-value* of the opponent! For example, male rats in a restraining tube attack *completely anesthetised* conspecifics as a function of the intensity of tail-shock [50]. It is important, yet completely unknown, whether similar mechanisms can also exacerbate human conflict. The final example is **defensive inhibition**: Under certain conditions social/predator threats will trigger a ***freezing reflex***. In particular, while close threats tend to trigger *active* defensive responses such as attack, distal threats reliably trigger a *passive* defensive response[24]. It is completely unknown whether this behavioural inhibition can undermine goal-directed responses to social conflict in humans. This risk might arise in any situation where the best response is proactive but is overridden by an inhibitory reflex (like a rabbit in the headlights).

What are the evolutionary obstacles to optimal conflict management? Which neurobiological mechanisms promote or undermine success? The answer to both these questions is largely unknown because there are currently no biologically informed interactive paradigms for studying human defensive behaviour. We will therefore use novel game-theoretically inspired social interaction tasks. These 'games' will be designed such that the specific costs of Pavlovian defensive responses can be estimated from real behavioural data. Crucially, this enables us to estimate individual differences in vulnerability to Pavlovian defensive biases and relate this to risk factors: both neuronal indices of subcortical (e.g. midbrain) responsiveness and preclinical questionnaire measures of defensive (anxiety) disorders.

1.2. Detailed research plan

The purpose of this project is to evaluate the personal and social costs of evolved defensive responses to social conflict. We will also examine the neuronal basis of these responses using fMRI recording methods. To achieve this goal, we will first establish new interactive learning paradigms in the social domain which can be used in combination with fMRI (i.e., N interacting subjects, one scanned by fMRI). We will also measure hormonal and autonomic stress responses.

These data will be used for the conventional analyses of the brain activity data as well as for the computational models where they will inform subject-specific priors on parameters encoding synaptic plasticity. The fMRI data will be analysed using statistical parametric mapping (SPM). In addition to modelling the factorial structure of the learning paradigm, trial-by-trial predictions from the computational model will be used to specify a general linear model. Regions of a priori interest include periaqueductal grey and amygdala. Further analyses will examine whether detailed quantitative models of defensive learning can explain additional fMRI and behavioural variation.

Specific aims

1. Do preclinical risk-factors predict vulnerability to costly social conflict in the lab?
2. Do the midbrain neuronal networks implementing non-social Pavlovian responses mediate this bias[46,51]?

Which investigations and experiments are necessary to achieve the specific aims?

To begin, we will conduct four experiments. One behavioural and one fMRI study in each of two domains: **defensive attack and defensive inhibition**. We have already completed initial pilots in both these domains to confirm the feasibility of these experiments.

Defensive attack

STUDY 1. In the first pilot study, subjects played a classical game of conflict over scarce resources. First they completed a memory/IQ task (Figure 1). Then they were given 25 CHF before being randomly and anonymously paired to different opponents. Most importantly, subjects then simultaneously decided whether or not to compete on the same memory/IQ task. If both competed, the winner was determined by their relative IQ. The winner gained 10CHF the looser lost 10 CHF. If neither competed then a coin was flipped and the winner took 10 CHF. If one player competed and the other did not, then the former won 10 CHF uncontested. To aid each decision, information on the relative performance was supplied: In principle this information could have been used to reach the game-theoretically optimal choice. Specifically a mixed equilibrium exists at

$$\left(\frac{V}{2\theta_1 V - V + 2AC\theta_1}, \frac{V}{V + 2AC - 2\theta_1 V - 2AC\theta_1}\right)$$

$$\text{where} \quad \frac{V}{V + AC} < \theta_1 < \frac{AC}{V + AC}$$

Where V is the value of the prize (10CH), C is the cost of loosing a conflict (10 CHF), θ_1 is the relative IQ and A is a loss aversion parameter. Intuitvely, subjects with a better test-score that their partener should compete more. We found that subjects' competitiveness did indeed strongly depend on the θ_1, indicating that subjects' based their conflict behaviour on a relevant social dominance parameter (Figure 1).

We then asked if behavioural responses to social conflict were biased by *irrelevant but evolutionarily significant* displays of social dominance: i.e. do such displays provoke costly **defensive attack**? To do this, we labelled the response option 'compete' with an angry face and the response option 'not compete' with a neutral face or vice versa (these players always played against someone who did not know about or observe faces). Our results show that the mere presence of angry face increases conflict. This fascinating result contradicts the prominent theory that social-dominance signalling functions to *reduce* unnecessary costs of conflict[52]. We have succeeded in establishing the technology for multi-person pain stimulation in order to examine if acute pain stressors modulate this aspect on real social interactions.

STUDY 2: We will adapt the above paradigm for fMRI imaging to examine whether subcortical responses to irrelevant social dominance cues can predict between-subject variability in costly behavioural responses. We hypothesize that an individual's subcortical BOLD sensitivity to evolutionarily important stimuli – e.g. angry faces and/or pain - predicts more defensive responses in the presence of that irrelevant stimulus.

The subjects to be investigated in this research project will be in the nonclinical healthy range for psychiatric symptoms. From this foundation, clinical populations can be investigated in the future (after completion of the present project), such as patients with anxiety-disorders whose symptoms point to exaggerated midbrain reactivity. In the long run this paradigm will serve as a useful assay to examine sensitivity of defensive attack to classic modulators of fear learning and expression (i.e. benzodiazepines or 5HT agonists which inhibit defensive strike in non-human animals [53]).

Defensive behavioural inhibition

STUDY 3: (See figure 2) In a second pilot we asked if subjects were unduly inhibited when facing distant social threats and if this inhibition undermined their response to conflict. In this simple game we showed that evolutionarily hardwired behaviours partly influence the winner of human contests. In our game of 'catch' PREDATOR must catch PREY to gain reward: PREY must avoid this in order to offset punishment. Players are positioned in one of two rooms and must simultaneously choose whether to enter the opponent's room or to stay put (see Figure 2). Because any predictability can easily be exploited by one's opponent, the best instrumental strategy is for each player to act randomly i.e. move with probability ½. In this Nash equilibrium, PREY must have no bias towards either active or passive avoidance: similarly for PREDATOR's active/passive approach. We hypothesised that such *goal-directed responses* would be undermined by primitive *Pavlovian responses*, involuntary behavioural reactions to the expected rewards and punishments of the game. Specifically, abundant animal work indicates that the presence of a distal predator can potently *inhibit* prey behaviour[1] while the prospect of reward more generally *activates* predator behaviour. If such stereotyped behaviours arise in human conflicts, our PREY may be paralyzed with inactivity, staying put and succumbing to an active PREDATOR. Our results points to a bias from Nash Equilibrium towards a 'Pavlovian equilibrium' at (NO GO, GO). Figure 2 displays results from 27 pairs and shows highly significant bias towards costly Pavlovian behavioural inhibition which cannot be explained by a long list of alternative hypotheses (see Figure 2 legend for a brief summary).

[1] 'unconditioned' or 'conditioned' punishments more generally

STUDY 4: We will extend this task by measuring concurrent neuronal responses in the fMRI. This permits us to relate social behaviour in this task to a large neuroscience literature on active versus passive avoidance of non-social threats as well as a literature on behavioural activation and inhibition. These dimensions are key to some current conceptualizations of personality[24]. We will then attempt to predict individual behaviour from fMRI indices and indices of preclinical vulnerability (to exaggerated defensive affect).

Which methods are at my disposal?

1. Neuroimaging technologies that are already optimized for social experiments. The Laboratory for Social and Neural Systems (SNS) is one of few in the world with these facilities.
2. Periaqueductal grey and other midbrain structures implicated in defensive instincts are small and suffer from low fMRI signal-to-noise. To overcome this, I will have unique access to the host institution's 7 Tesla MRI scanner. Such high-field MRI facilities presently exist in only a few places..
3. State-of-the-art eye, fully equipped tracking laboratory with in-house expertise in visual behaviour analysis.
4. Cluster computing facilities for computational simulations and efficient data-analysis.
5. Expert consultants in computational theory, game theory, social cognition, imaging analysis, experimental design.

- Information on support personnel: State the planned work of support personnel and justify the employment

The scope of the experimental work needed for this project requires a second person, in addition to myself, for data collection and analysis. As experimental design and data analyses require fairly advanced skills in programming, statistics and scientific insight, a research assistant will not be sufficient and a PhD student is critically required. She/he will focus on conducting the already-tested behavioural paradigms in the MRI (i.e. **STUDIES 2,4)**. I will train the student in fMRI acquisition, data management in year 1. In subsequent years, primary acquisition and management will be in his/her hands. I will develop compact quantitative theories of behaviour and focus on model-based data analysis. The student will be encouraged to develop extension of behavioural pilots to pharmacology. The student will also benefit from the weekly meetings and teaching seminars (SPM courses, DCM etc.) at the TNU.

1.3. Timetable for the whole project

Milestones and Work Plan

Year 1: Defensive attack

Months 1-2:	Development and programming of novel behavioural social learning paradigms
Month 3:	Behavioural study using the new Defensive attack social learning paradigm
Months 4-5:	Analysis and modelling of behavioural data
Months 6-7:	Preparation of behavioural manuscript for publication **(STUDY 1)**
Months 8:	Preparation of simultaneous fMRI studies
Months 9-10:	fMRI studies: data acquisition, SPM analysis
Months 11-12:	Preparation of manuscript for publication **(STUDY 2)**

Year 2: Defensive submission

Months 1-2:	Development and programming of novel behavioural social learning paradigms
Month 3:	Behavioural study using the new paradigm
Months 4-5:	Analysis and modelling of behavioural data
Months 6-7:	Preparation of behavioural manuscript for publication **(STUDY 3)**
Months 8:	Preparation of simultaneous fMRI studies
Months 9-10:	fMRI studies: data acquisition, SPM analysis
Months 11-12:	Preparation of manuscript for publication **(STUDY 4)**

1.4. Significance of the planned research

Human stress is the biggest contemporary challenge to quality of life. Implicated in a staggering number of stress-related conditions, from cardiovascular to psychiatric illness, it is the most important public health issue[54]. Because social events such as conflict can create and amplify psychological stress and its endocrine indices[34,55], we will experimentally examine novel mechanisms that increase exposure to social conflict and stressors. This connection makes our work relevant to a large and active field of stress research. In particular, it is of special relevance to the study of stress-related psychiatric illness. Clinical theorists have long speculated, but not tested, a Pavlovian basis for socially inappropriate behaviour.

A quantitative theory of *real human defensive behaviour* is necessary for understanding social conflict and the distribution of power in societies. Game theory, which makes unreasonable demands on human cognition, must be informed and constrained by neurobiological, psychological and ethological facts. In this way our work is broadly relevant to social science and economics.

There is an established literature on the neuronal basis of impulsive responses to reward. Our work will contribute much-needed insights to neuroscientific theories of impulsive responses to punishment.

2. References

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FIGURES

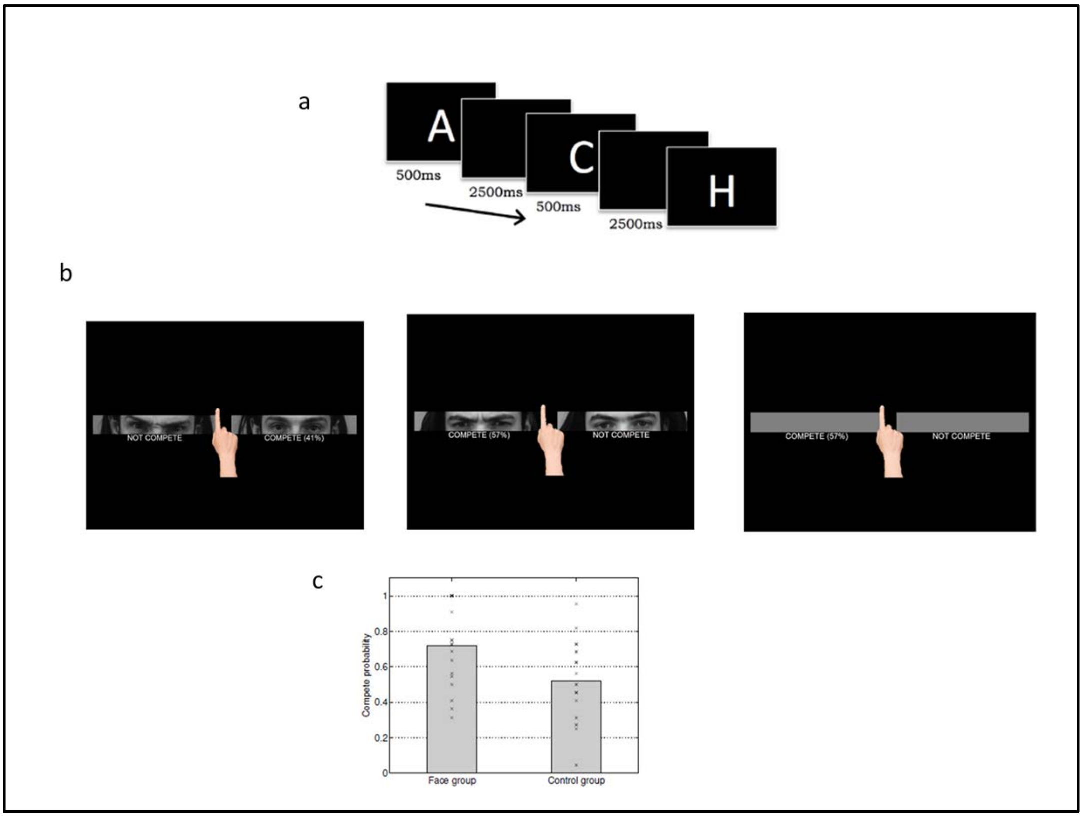

Figure 1. Preliminary evidence for costly *defensive attack*. a. 24 subjects first simultaneously completed the n-back memory/IQ test. They were then randomised to one of three conditions (b) and asked to choose whether to compete with a randomly assigned partner or not on this same test. Relevant, relative-performance information was provided to aid this choice. For some subjects, irrelevant aggressive cues were present at the time of choice. c. Subjects compete more and suffer more unnecessary costs in the presence of these irrelevant aggressive cues, even when they know such cues are completely uninformative and do not depict their partner. From further conditions (not depicted) we conclude that this 'impulsive' response is driven specifically by angry faces and we rule out four alternative explanations for this effect.

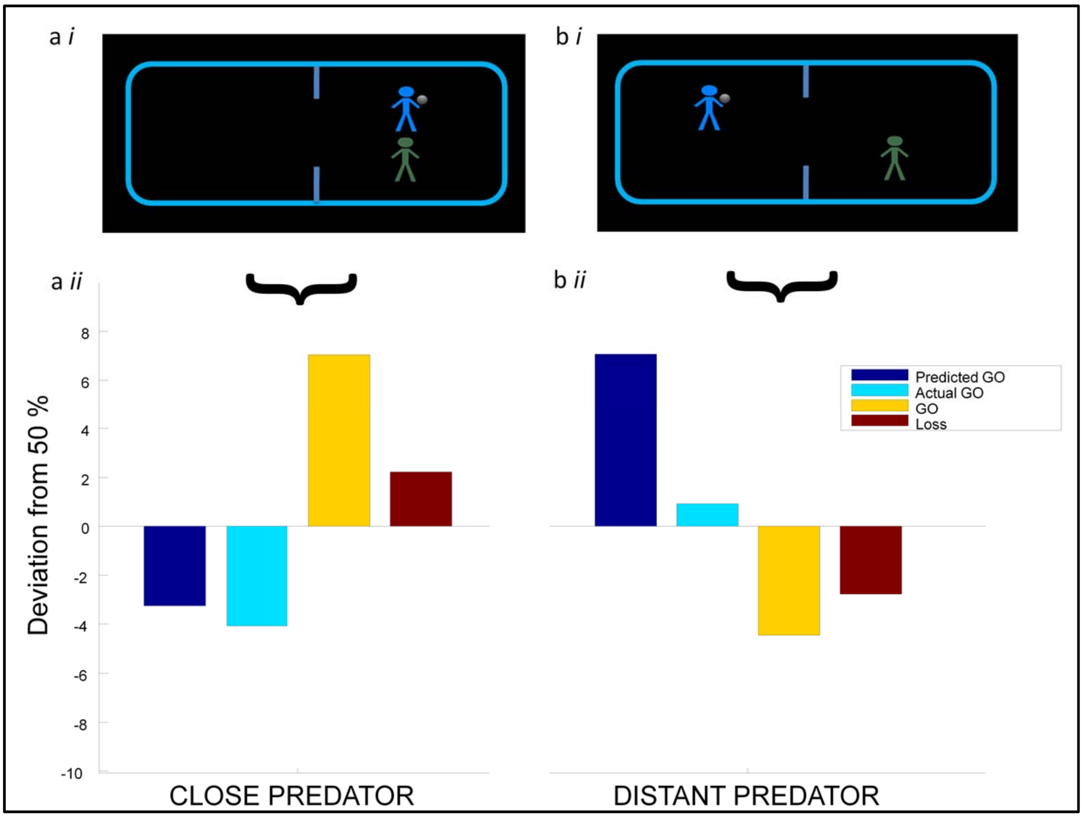

Figure 2. Preliminary evidence for costly defensive inhibition. a*i* and b*i* depict two initial conditions for a game of 'catch' in which both subjects simultaneously decide whether to stay or move. a*i*. The top, blue player is prey: She holds a money token that will be lost if the bottom, green player catches her (ends up in the same room). Her goal is to avoid the predator in order to retain the money token. Conversely the predator stands to win from catching the prey. In the condition depicted in a*i*, the prey faces a *close* predator threat. In b*i* she faces a *distal* threat. a*ii*. The first bar in a*ii* illustrates the preys' expectation about what the predator will do (GO probability), averaged over pilot subjects. The next bar in a*ii* illustrates what the predator *actually does* on average. This confirms that prey have accurate beliefs. The next bar in a*ii* shows the *prey*'s behaviour and associated costs (how often prey loose money). Notice that prey facing a distant predator move less and face higher average losses despite reporting that they *know* the predator is more likely to come. These data and additional analyses (not reported here) strongly implicate a kind of irrational freezing in this dysfunctional approach to the conflict. We aim to understand the biology of this effect within this paradigm.

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Justin Renshaw Chumbley

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in Modelling Biological Complexity

Provost and President, University College London

Vice-Chancellor

1 November 2006

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JUSTIN RENSHAW CHUMBLEY

having satisfactorily completed the approved course of study and the prescribed assessment has this day been awarded the degree of

Doctor of Philosophy

Date of award: 28 January 2010

Professor Malcolm Grant
President and Provost
University College London

000000013556-1

UNIVERSITY OF LONDON

Imperial College of Science, Technology and Medicine

Justin Renshaw Chumbley

having completed the approved course of study and passed the examinations has this day been admitted by Imperial College of Science, Technology and Medicine to the University of London Degree of

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in Neuroscience

Richard B Sykes

Rector, Imperial College of Science, Technology and Medicine

Vice-Chancellor

1 November 2002

UNIVERSITY OF LONDON

University College London

Justin Renshaw Chumbley

having completed the approved course of study and passed the examinations has this day been admitted by University College London to the University of London Degree of

MASTER OF SCIENCE

in Statistics

Provost and President, University College London

Vice-Chancellor

1 November 2005

Confirmation of access to existing infrastructure

In his reference for me ***Ernst Fehr*** (host for the project) will confirm my access to all existing SNS infrastructure in order to carry out your project.

A Specific note to ***Faculty of Economics, Business Administration and IT***

The application guidelines for Forschungskredit 2013 in the Faculty of Economics, Business Administration and IT invites me to explain why I did not apply by last year (i.e. by age 34 with 2 years postdoc). In response, I did not know of this avenue last year and was still developing some of the technologies prerequisite to this rather elaborate, interdisciplinary project.