**Do fight-or-flight reflexes derail human conflict?**

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Evolution has provided all animals with hard-wired “stress responses”, including preprogrammed behavioral [[1](#_ENREF_1)] and hormonal [[2](#_ENREF_2)] defensive reactions to social conflict. Despite natural selection, the *hormonal stress response* (HSR) can have disastrous consequences: psychosocial stress is a number one killer in the west [[3](#_ENREF_3)]. In contrast, the impact and cost of *behavioral stress responses* (BSRs) for human welfare is poorly understood.

This project will examine the impact of BSRs on human conflict. To experimentally manipulate BSRs during social interaction, we will vary subjects’ exposure to threat stimuli as they play strategic games on a computer network. We hypothesize these experimental threats trigger defensive BSRs, causing subjects to depart from ideal defensive behavior, as defined game-theoretically. We hypothesize that this unhelpful defensiveness is more common among individuals with *defensive personality traits* [[4](#_ENREF_4),[5](#_ENREF_5),[6](#_ENREF_6),[7](#_ENREF_7),[8](#_ENREF_8),[9](#_ENREF_9),[10](#_ENREF_10),[11](#_ENREF_11)]. There are two parts to the proposed project.

1. **Behavioral experiments:** In pilot studies I have already measured defensive strategies in bilateral conflicts. These data are the first of their kind and suggest that BSRs do indeed compromise strategic behavior. I will replicate/extend these results before analyzing the underlying biology.
2. **The basis of individual differences:** I will correlate individual BSR effects with other measures of stress responsiveness: hormonal (cortisol) and electrodermal reactivity, and personality measures of defensive affect. Using fMRI I will concurrently measure *neuronal* responses during conflict. I aim to predict individual differences in defensive social behavior from the reactivity of subcortical systems mediating BSRs (e.g. periaqueductal grey, central amygdala).

This work sets the foundation for identifying expression of these pathogenic mechanisms in clinically distressed versus healthy populations.

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1. Research Plan

## 1.1. Statement of research

**General context**

Faced with potential conflict, it pays to consider the merits of each available strategy and anticipate the opponent’s likely response [[12](#_ENREF_12),[13](#_ENREF_13)]. In contrast, animal conflicts are partly governed by hardwired defensive tactics: behavioral stress responses (BSRs), including fight, flight and freeze [[6](#_ENREF_6),[7](#_ENREF_7),[14](#_ENREF_14),[15](#_ENREF_15),[16](#_ENREF_16),[17](#_ENREF_17),[18](#_ENREF_18),[19](#_ENREF_19),[20](#_ENREF_20),[21](#_ENREF_21),[22](#_ENREF_22),[23](#_ENREF_23)]. While these ‘Pavlovian’ responses were selected by evolution, their reflexive character opens them to exploitation by real [[24](#_ENREF_24)] and artificial [[25](#_ENREF_25),[26](#_ENREF_26)] threats, a phenomena examined in theory [[27](#_ENREF_27)], ethology [[28](#_ENREF_28)] and experiment [[29](#_ENREF_29)].

There is speculation that BSRs also affect the outcome of human conflict, particularly via vulnerable individuals [[4](#_ENREF_4),[5](#_ENREF_5),[6](#_ENREF_6),[7](#_ENREF_7),[8](#_ENREF_8)]. We will ask whether stressors influence the outcome of strategic conflict by triggering BSRs. Our hypotheses are derived from animal work showing that *threat proximity* – ones distance from the opponent – tips the balance between the **freeze** and **flight** responses. Specifically, *close threats trigger flight*, while *distant threats trigger freezing* [[30](#_ENREF_30)]. We look for evidence that this evolutionary bias can systematically derail a person’s defensive strategy.

**Specific aims**

1. Do defensive compulsions to flee and freeze impact human conflict?
2. Is this tendency higher among defensive personalities?
3. Do midbrain networks implementing BSRs mediate this variation [[1](#_ENREF_1),[31](#_ENREF_31)]?

**The experiments which will achieve these specific aims**

We will conduct two experiments using a novel, interactive GO-NOGO paradigm: One behavioral and one fMRI study. We have already completed initial pilots to confirm the feasibility of these experiments.

### Defensive behavioral inhibition

**STUDY 1:** In this pilot we examined whether subjects systematically changed their defensive strategy according to their opponent’s proximity, even though this strategy was counterproductive. In our game of ‘catch’ PREDATOR must catch PREY, who must avoid PREDATOR (See Figure 1). Players stand in one of two rooms and simultaneously choose whether to stay or move (see Figure 1). Because predictability can be exploited by ones opponent, the Nash equilibrium strategy is for each player is to act randomly, i.e. move with probability ½, regardless of threat proximity. In contrast, we hypothesize that threat proximity would bias behavior toward the BSR: freezing to distal opponents and fleeing proximal ones.

Animals also show non-defensive, or appetitive, Pavlovian responses. For example, expected reward tends to *activate* behavior. We therefore also hypothesized biased predator behavior. In the context of Figure 1C for example, these two biases should combine to make PREY freeze and succumb to an active PREDATOR. Our results point to such a bias from Nash Equilibrium towards a ‘Pavlovian equilibrium’ at (NO GO, GO). Figure 1 displays results from 27 pairs and shows highly significant bias towards costly freezing which cannot be explained by various alternative hypotheses (see Figure 1 legend for a brief summary). This suggests that behavioral biases observed in animals can predict the outcome of human conflict beyond game theory. We will replicate this study and consider control studies to exclude alternative explanations.

**STUDY 2:** We will extend this task by measuring concurrent neuronal responses in the fMRI. This permits us to relate our social task to large neuroscience literatures on active versus passive avoidance and behavioral activation and inhibition. We will then attempt to predict individual behavior from fMRI indices and personality measures of defensive affect [[30](#_ENREF_30)]. We hypothesize that subcortical BOLD responses to threat predict the impact of errant BSRs.

These data will be used for the conventional analyses of the brain activity data. The fMRI data will be analyzed using statistical parametric mapping (SPM). 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 behavioral variation.

**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 behavior 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.

## 1.3. Timetable for the project

**Milestones and Work Plan**

**Year 1: Defensive attack**

Months 1-2: Behavioral study using the new Defensive attack social learning paradigm

Month 3-4: Analysis and modelling of behavioral data

Months 5-6: Preparation of behavioral manuscript for publication **(STUDY 1)**

Months 7-8: Preparation of simultaneous fMRI studies

Months 9-10: fMRI studies: data acquisition, SPM analysis

Months 11-12: Analysis and Preparation of manuscript for publication **(STUDY 2)**

## 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 [[3](#_ENREF_3)]. Because social events such as conflict can create and amplify psychological stress and its endocrine indices [[32](#_ENREF_32),[33](#_ENREF_33)], we will experimentally examine novel mechanisms that derail conflict, increasing social 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, an evolved basis for some socially inappropriate defensive behavior.

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.

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 [[34](#_ENREF_34)]).

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A description...

**Figure 1. Preliminary evidence for defensive BSRs.** A and C depict two initial conditions for a game of ‘catch’ in which both subjects simultaneously decide whether to stay or move. A. 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. Conversely the PREDATOR stands to win from catching the prey. In the condition depicted in A, prey faces a close threat. In D she faces a distal threat. B. The first bar gives the preys’ expectation about what the predator will do (GO probability), averaged over pilot subjects. The second bar gives what the predator actually does on average. This confirms that prey have accurate beliefs. The next bar in B shows the prey’s behaviour and associated financial loss. Notice that prey facing a distant predator freeze and face higher losses, despite knowing the predator will likely approach them. These data and additional analyses (not reported here) implicate BSRs. We aim to understand the biology of this effect within this paradigm.