Research Articles: Behavioral/Cognitive

Disentangling hippocampal and amygdala contribution to human anxiety-like behaviour

https://doi.org/10.1523/JNEUROSCI.0412-19.2019

Cite as: J. Neurosci 2019; 10.1523/JNEUROSCI.0412-19.2019
Received: 21 February 2019
Revised: 25 August 2019
Accepted: 29 August 2019

This Early Release article has been peer-reviewed and accepted, but has not been through the composition and copyediting processes. The final version may differ slightly in style or formatting and will contain links to any extended data.

Alerts: Sign up at www.jneurosci.org/alerts to receive customized email alerts when the fully formatted version of this article is published.
Disentangling hippocampal and amygdala
collection to human anxiety-like
behaviour

Running head: Hippocampus and amygdala in human anxiety-like behaviour

Dominik R Bach1,2 *Martina Hoffmann3, Carsten Finke3,4, Rene Hurlemann5,6, Christoph J. Ploner3

1Computational Psychiatry Research, Department of Psychiatry, Psychotherapy, and
Psychosomatics, University of Zurich, Switzerland
2Wellcome Centre for Human Neuroimaging and Max Planck/UCL Centre for
Computational Psychiatry and Ageing Research, University College London, UK
3Department of Neurology, Charité – Universitätsmedizin Berlin Germany
4Berlin School of Mind and Brain, Humboldt-Universität zu Berlin, Germany
5Department of Psychiatry & Division of Medical Psychology, University of Bonn,
Germany
6Department of Psychiatry, University of Oldenburg Medical Campus, Bad Zwischenahn,
Germany

*Corresponding author: Department of Psychiatry, Psychotherapy, and Psychosomatics;
Psychiatric University Hospital Zurich; Lenggstrasse 31; CH-8032 Zurich;
dominik.bach@uzh.ch

Figures: 5
Tables: 3

Introduction: 648 words
Discussion: 1294 words
Abstract

Anxiety comprises a suite of behaviours to deal with potential threat and is often modelled in approach-avoidance conflict tasks. Collectively, these tests constitute a predominant pre-clinical model of anxiety disorder. A body of evidence suggest that both ventral hippocampus and amygdala lesions impair anxiety-like behaviour, but the relative contribution of these two structures is unclear. A possible reason is that approach-avoidance conflict tasks involve a series of decisions and actions, which may be controlled by distinct neural mechanisms that are difficult to disentangle from behavioural readouts. Here, we capitalise on a human approach/avoidance conflict test, implemented as computer game, that separately measures several action components. We investigate three patients of both sexes with unspecific unilateral medial temporal lobe (MTL) damage, one male with selective bilateral hippocampal (HC) and one female with selective bilateral amygdala lesions, and compare them to matched controls. MTL and selective HC lesions, but not selective amygdala lesions, increased approach decision when possible loss was high. In contrast, MTL and selective amygdala lesions, but not selective HC lesions, increased return latency. Additionally, selective HC and selective amygdala lesions reduced approach latency. In a task targeted at revealing subjective assumptions about the structure of the computer game, MTL and selective HC lesions impacted on reaction time generation but not on the subjective task structure. We conclude that deciding to approach reward under threat relies on hippocampus but not amygdala, while vigour of returning to safety depends on amygdala but not on hippocampus.
Significance statement

Approach/avoidance conflict tests are widely investigated in rodents, and increasingly in humans, to understand the neural basis of anxiety-like behaviour. However, the contribution of the most relevant brain regions - ventral hippocampus and amygdala - is incompletely understood. We use a human computerised test that separates different action components and find that hippocampus, but not amygdala, lesions impair approach decisions, while amygdala, but not hippocampus, lesions impair the vigour of return to safety.
Introduction

Appropriate behaviour in the face of conflicting goals is key to arbitrating many biological scenarios, and it is particularly challenging when threat is involved such as during foraging and exploration under predation. A laboratory model of this situation is provided by approach/avoidance conflict tests (Calhoon and Tye, 2015), often regarded as reflecting aspects of clinical anxiety in humans (Gray and McNaughton, 2000; Calhoon and Tye, 2015; Bach et al., 2018). A body of literature demonstrate that the ventral (in rodents) or anterior (in humans) hippocampus (HC) is involved in behavioural control in such tests (see Gray and McNaughton, 2000; Ito and Lee, 2016; Kirlic et al., 2017 for comprehensive reviews), and somewhat less consistently, the amygdala (Kirlic et al., 2017). In humans, we have previously shown that degenerative HC (Bach et al., 2014b) and amygdala lesions (Korn et al., 2017) impact on an anxiolytic-sensitive (Korn et al., 2017; Bach et al., 2018) approach/avoidance test. Yet, the mechanistic function of these areas remains debated (Ito and Lee, 2016). Beyond a well-known role of the HC for spatial cognition and memory, several suggestions for its function in approach/avoidance conflict have been put forward: that ventral HC is involved in behavioural inhibition when conflict is detected (Bannerman et al., 2014), that it represents threat aspects of the situation, the removal of which would reduce threat-related behaviour (Gray and McNaughton, 2000), and/or that it inhibits representation of reward aspects (Ito and Lee, 2016) with possibly distinct roles for HC subfields (Schumacher et al., 2018).

Notably, many classic approach/avoidance tests share the limitation that their behavioural readouts collapse several distinct actions. This is particularly the case for ethological tests such as elevated plus maze (EPM) (Pellow et al., 1985) or open field test
(OFT) (Montgomery, 1955), which combine several components of approach behaviour as well as withdrawal from danger, and decision processes, into a small number of readouts (Rodgers et al., 1997). Some of these actions such as active avoidance or escape are not known to require hippocampus in non-conflict situations (LeDoux et al., 2017; Evans et al., 2018), but a direct comparison is difficult. Our previously proposed human approach/avoidance test (Bach et al., 2014b), a computerised translation of open field test, is imbued with the same problems.

In contrast, operant conflict tests in rodents (Geller and Seifter, 1960; Vogel et al., 1971) and non-human primates (Chudasama et al., 2008; Amemori et al., 2015) in principle allow separating action components (see Oberrauch et al. 2019 for an example in mice). Here, we capitalise on a human operant conflict test (Bach, 2015), which measures a decision to approach (action), the vigour with which this action is implemented (approach latency), and the vigour of the retreat to safety (return latency). All these behavioural components are influenced by the probability of virtual predation (threat level) and the possible loss involved: healthy humans reduce approach, delay approach, and accelerate return, when the situation is more dangerous (Bach, 2015). While reducing approach and accelerating return is reward-maximising, delaying approach is not. However, it reminisces novelty-suppressed feeding (Britton and Britton, 1981), another rodent approach/avoidance test, and can be explained under particular subjective assumptions about the task parameters (Bach, 2015, 2017). Furthermore, we have previously shown with magnetoencephalography that hippocampus may be involved in behaviour in this task (Khemka et al., 2017).

Here, we investigated three patients with unilateral medial temporal lobe (MTL) lesions, one patient with selective bilateral HC damage, and one patient with selective bilateral amygdala lesion. We hypothesised that hippocampus, but not amygdala, lesions impact
on the decision to approach. In our previous approach/avoidance conflict test, behaviour was particularly impaired by HC lesions and anxiolytics when potential loss was high (Bach et al., 2014b; Korn et al., 2017; Bach et al., 2018), such that we expected here a lesion x potential loss interaction. Based on the amygdala’s role in non-conflict active avoidance (LeDoux et al., 2017), we also hypothesised that amygdala but not hippocampus lesions impact on return to safety under conflict.
Methods

Participants. We recruited three patients with post-surgical unilateral medial temporal lobe (MTL) lesions affecting hippocampus, amygdala and adjacent neocortex, together with 10 control participants; one patient with highly selective bilateral hippocampus (HC) lesions and 9 control participants; as well as one patient with bilateral selective amygdala lesions due to Urbach-Wiethe syndrome, together with 26 controls (table 1). All controls were age- and sex-matched.

Post-surgical MTL lesions resulted from resection of benign brain tumors in all three patients and always affected the right amygdala, anterior hippocampus, entorhinal cortex and parts of perirhinal cortex. The parahippocampal cortex was spared in all patients. Onset of presurgical symptoms was during adulthood. All patients had already participated in previous investigations of our group (see (Braun et al., 2008; Finke et al., 2008; Esfahani-Bayerl et al., 2016) for clinical details, imaging, and neuropsychological findings). Patients suffered from mild visuospatial memory deficits but were fully independent in daily life activities.

In the HC patient, exceptional selective bilateral HC lesions resulted from autoimmune encephalitis. In this patient, both hippocampi were equally affected across the entire rostro-caudal extent. Entorhinal cortex, perirhinal cortex and parahippocampal cortex were completely spared (see (Esfahani-Bayerl et al., 2019) for clinical details and neuropsychological findings). Similar to the cases in Rempel-Clower et al. (1996), this patient suffered from a retro- and anterograde amnesic syndrome that severely affected autobiographical events, verbal, visual and spatial memory, while some other memory domains were spared or less affected (e.g. memory for music and faces).

MTL and HC patients were tested in 2016 at Charité University Hospital in Berlin.
In the amygdala patient (previously labelled BG, or patient 2, (Becker et al., 2012)), lesions encompassed most of bilateral amygdalae and left both hippocampi almost unaffected. Neuropsychology and imaging findings for BG have been extensively covered in previous reports (Talmi et al., 2010; Bach et al., 2011; Becker et al., 2012; Bach et al., 2013, 2014a; Korn et al., 2017). The patient is impaired in anterograde and retrograde interference of emotional pictures on memory (Hurlemann et al., 2007), phonemic fluency and short-term concentration (Talmi et al., 2010), free verbal recognition of fearful faces, startle potentiation by threat-related scenes, social network size (Becker et al., 2012), and prioritisation of angry over happy face expression (Bach et al., 2014a).

The patient was tested in 2017 at age 43 at the University Hospital in Bonn; her twin sister was not tested. All control participants were independent from previous studies using the same or similar setups (Bach, 2015, 2017; Khemka et al., 2017). From the amygdala control group, we excluded two participants due to low performance (ie. low number of trials in which they approached the token and survived the virtual predator): their performance was more than 4 standard deviations below the mean of the rest of this control group, around 2 standard deviations below the next worst performing participant of the rest of the control group, and smaller than any patient or control participant in the hippocampus sample. The study was in full accordance with the Declaration of Helsinki and approved by the respective local research ethics committees.
### Table 1. Patient and lesion characteristics.

| Patient | Age | Sex | Lesion | Etiology | Clinical note |
|---------|-----|-----|--------|----------|---------------|
| MTL 1  | 51  | f   | AMY: + | HC: + | ERC: + | PRC: + | PRC: - | PRC: - | PRC: - | PRC: - | Fibrillary astrocytoma, symptoms < 1 year before resection, testing 133 months after surgery | No relapse, seizure free, visuospatial memory deficits |
| MTL 2  | 52  | m   | AMY: + | HC: + | ERC: ++ | PRC: ++ | PRC: - | PRC: - | PRC: - | PRC: - | Neuroepithelial tumor, symptoms 1 year before resection, testing 197 months after surgery | No relapse, seizure free, visuospatial memory deficits |
| MTL 3  | 41  | f   | AMY: + | HC: + | ERC: ++ | PRC: ++ | PRC: - | PRC: - | PRC: - | PRC: - | Epidermoid tumor, symptoms 3 years before resection, testing 152 months after surgery | No relapse, seizure free, visuospatial memory deficits |
| HC 25  | m   | -   | AMY: +++ | HC: - | ERC: - | PRC: +++ | PRC: - | PRC: - | PRC: - | PRC: - | Autoimmune encephalitis, onset ten days before testing | Severe amnesic syndrome |
| Amy 43  | f   | (+) | AMY: + | HC: + | ERC: + | PRC: (+) | PRC: - | PRC: - | PRC: - | PRC: - | Congenital Urbach-Werthe syndrome (de novo mutation), testing 31 years after first symptoms | Seizure free, social and affective deficits |
**Figure 1**: Behavioural task. On each trial, a human player (green triangle) rests in a safe place on the bottom of grid, while a “predator” is sleeping at the top (gray circle). On each epoch, up to six successive reward tokens (yellow rhombi) appear. To obtain a token, the player uses the left/right cursor keys to move out of the safe place and back. The coloured frame indicates the threat level of the sleeping predator with color/threat association balanced across subjects. When caught, all tokens are lost. Potential loss is the number of tokens already collected on this epoch. (p: probability to get caught per 100 ms outside of safe place)

**Design & procedure: approach/avoidance conflict task.** This operant conflict test kept approach incentive constant and varied avoidance incentives in a 3×6 factorial design with the within-subjects factors "threat level" (wake-up probability of the virtual predator: low/medium/high) and "possible loss" (0-5 tokens). Participants played 4 (MTL/HC lesion/controls) or 6 (amygdala lesion/controls) blocks of 45 successive epochs of a previously published computer game (Bach, 2015) on a 2x2 grid, presented with ~4° vertical visual angle on a standard LCD monitor (figure 1). To allow direct comparison between MTL/HC and amygdala lesions, with different numbers of task blocks, only the first 4 blocks were included in the analysis. The human player was controlled with the left/right cursor keys on a standard computer keyboard and could move between the lower three grid blocks any time unless caught by the predator. Each move between adjacent grid blocks required a single key press. The player started each epoch in the 'safe' bottom grid block. In each epoch, a sequence of up to 6 reward tokens appeared at random time points in a random (left/right) location. The player could
decide each time whether or not to approach and collect the token by moving to its location. Participants received a fixed payment and an additional reward for the number of retained tokens of one randomly drawn epoch at the end of the experiment. A "sleeping predator" was waiting above the token and could become active if the human player was outside the safe place, with a probability per time unit that was constant over time ($p_1=0.1$, $p_2=0.2$, and $p_3=0.3$, for the three predators, per 100 ms). Actual catch rates depend on participants' return latencies (see figure 3). It would then "eat" the human player, and all previously collected reward tokens from this epoch were removed. Once the predator was active, the human player had no possibility to escape. After catching the player, the active predator stayed visible on the screen for the remaining time of the epoch while the human player had to wait. The token stayed on the screen and could be collected for a random interval drawn from an exponential distribution with a mean of 1.25 s. If the player did not collect the token, then the token disappeared after this interval. After the pre-determined disappearance time, a waiting interval with random duration started (drawn from the same exponential distribution plus 500 ms), before the next token came on the screen or the epoch ended.

Design & procedure: safe predator exposure task 2 (HC study). In blocks 5-6, participants in the HC study were given a different task on 36 epochs per block, randomly interspersed with 9 epochs of approach/avoidance conflict task 1. Task 1 epochs from these blocks were not included into the analysis to allow direct comparison with the amygdala lesion patient. The type of task was graphically signalled by a grey rhombus (approach/avoidance task) or a grey circle (safe predator exposure task) below the grid. The graphical setup of task 2 was exactly the same as in task 1, but participants could not move on the grid and always stayed in the safe place. They were
asked to "expose" the awake predator by pressing the cursor up key. If the predator was
awake at this point in time, it would turn red, and the next epoch would start. If the
predator was sleeping, it would turn black for 100 ms and the epoch would continue.
This feedback gave participants an opportunity to learn the experimental statistics,
according to which the probability of being awake was independent of time, or of token
appearance. On each epoch, the human player had 6 attempts to expose the predator,
after which the key was disabled until the epoch ended. Participants were explicitly
informed that the tokens could not be collected. The duration of the task depended on
participants’ behaviour: they could shorten the task by attempting to expose the
 predator independently from the tokens. One randomly selected epoch from task 2 was
rewarded at the end of the experiment; if the participant successfully exposed the
 predator, they gained as much as from collecting 2 tokens in task 1. The objective wake-
up probabilities of the three predators for each exposure attempt were $p_1 = 0.1$, $p_2 = 0.2$,
$p_3 = 0.3$, and constant over time.

Design & procedure: memory test. After the last trial, participants were asked, for
each of the three threat levels, to indicate how likely it was that they got caught if they
left the safe place. Participants were shown the grid with the frame colour, and asked to
make a rating on a visual analogue scale anchored with "0%" and "100%" (see figure 3).

Data analysis. All inference statistics were computed in the software R (www.r-
project.org). We first tested the entire control group's behaviour in the task to ensure
consistency with previous publications. We then compared the MTL lesion with its
control group in linear mixed effects (LME) model to identify potential consequences of
amygdala and/or hippocampus lesions. We then extracted respective coefficients and
compared the effect of MTL lesions with the effect of selective hippocampus or amygdala
lesions, to clarify the contribution of amygdala and hippocampus. Single-trial data for
approach and return latency are necessarily unbalanced because the number of data
points for each cell in the design depends on behavioural choices and on chance. This is
why LME models are more appropriate than a traditional ANOVA approach.

Decision to approach: Decision to approach was reconstructed by creating 6 data points
for each epoch, corresponding to the possibility of collecting six tokens. For each of
these six tokens, we scored 0 if the individual chose to collect less than this number of
tokens and 1 otherwise. Choices in epochs on which the player was caught cannot be
reconstructed and were therefore not analysed. The resulting single-trial data are
serially correlated by design. To reduce this correlation, they were averaged within
conditions, and we analysed the proportion of approach responses in a [2 (group) x] 3
(threat level) x 6 (potential loss) LME model with random subject intercept. Fixed-
effects F-tests were based on unpartitioned error variance and Satterthwaite
approximation to degrees of freedom which appropriately controls the false positive
rate (Luke, 2017) (using the R functions anova and lmerTest). We then applied
Greenhouse-Geisser correction for violations of multisphericity.

Approach and return latency: For each trial on which participant approached the token,
we extracted the approach latency, and if the player was not caught, also the return
latency. To avoid response latencies being biased by extreme values, they were only
analysed if they fell into response windows of 150 ms < approach latency < 2000 ms and
0 ms < return latency < 2000 ms, as in previous work (Bach, 2015, 2017). Most players
rarely collected the 6th token such that some design cells were empty and the
parameters could not be estimated reliably. Therefore, the 6th token was excluded for
all RT analysis. RT data on the single-trial level were analysed in a [2 (group) x] 3 (threat
level) × 5 (potential loss) LME model. We did not transform reaction times, as we had no a priori reason to do so, and a previous report demonstrated that analysis of log-transformed reaction times replicates analysis of raw RTs (Bach, 2015).

**Comparison between patients:** To compare selective and unselective lesions, we used an ordinal approach based on summary statistics, to avoid making strong distributional assumptions on the single-case level. We computed the single-subject summary statistic reflecting the group-level significant fixed effect in the LME (linear coefficient or overall mean). We then computed the percent rank of each patient within their respective control group. To compare one patient against a group of other patients, we used Crawford’s approach for dissociation (Crawford et al., 1998; Crawford and Garthwaite, 2005b, a). This tests a null hypothesis that the difference between two test scores (here relating to two patients) is drawn from the same distribution as the differences between pairs of control participants. In contrast to a purely descriptive approach, it allows inferential statements whether two patients’ positions in a population distribution are different (Crawford et al., 2003). We modified this approach to ordinal level, and allowed each patient to have its own control group. Thus, we created an ordinal bootstrapping test that compared the rank difference between two groups of patients with the rank differences observed in 10,000 simulations of two control groups of the same sizes as empirically used.

**Accounting for memory impairment and other confounds:** Because of the known role of HC for declarative memory, we note that any findings relating to threat level can potentially be explained by impairment to learn the colour-threat level association and do not directly speak to anxiety behaviour, different from findings relating to potential loss or overall group differences. We tested the impact of MTL lesions on subjective catch rate in a group (lesion/control) × threat level ANOVA, and in a group
lesion/control) x true catch rate LME model. To account for potential differences in the
overall subjective threat level (i.e. averaged across the three threat levels), we added this
as a covariate (crossed with within-subject factors) to LME models with significant
findings. Finally, we repeated all LMEs after adding potential confounds together with
the group factor (crossed with within-subjects factors) as covariate, namely years of
education, visual memory (Rey-Osterrieth Complex Figure Test: copy, immediate recall,
delayed recall (Shin et al., 2006)), and estimation of overall catch rate in the approach-
avoidance task.

Safe predator exposure task: We sought to determine whether participants’ responses
depended on the appearance of irrelevant tokens. To this end, we split the data into key
presses made before the first token appeared, and those made later. For key presses
after the first token, we computed the latency of each response with respect to the last
token that preceded it, and analysed the ensuing RT distributions. The distribution of
these responses was compared against two null distributions that test the null
hypotheses that key presses are unrelated to tokens with Kolmogoroff-Smirnoff (KS)
tests. For details on the derivation of these null distributions, see (Bach, 2017).

Differences between patients and controls were tested in a 2-sample KS-test, and a 2-
sample t-test on mean RT per participant.

To assess the most likely source of a RT difference between patients and controls, we fit
a previously derived reaction time model of the following form:

\[
p_{\text{cond}} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \frac{e^{-t^2/2}}{\sqrt{2}} \text{erfc}(\frac{t - \mu}{\sqrt{2\sigma^2}}) dt
\]

with

\[
p_{\text{exGauss}} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{\infty} \frac{e^{-t^2/2}}{\sqrt{2}} \text{erfc}(\frac{t - \mu}{\sqrt{2\sigma^2}}) dt
\]
Here, $T_2$ is the time point of the key press with respect to the last appearing token, and $\lambda$, $\mu$, $\sigma$, or $w$ are group parameters. We compared an implementation of this model with parameters shared between patients and control participants, and implementations with group-specific parameters for $\lambda$, $\mu$, $\sigma$, or $w$. Model parameters and likelihood were estimated using the in-built Matlab function `mle.m`. We quantified model evidence as Log Bayes Factors based on Bayesian Information Criterion (Raftery, 1995) ($LBF = 0.5 \times (BIC_{\text{ref}} - BIC)$ and considered an absolute $LBF$ difference $> 3$ as decisive, in analogy to classical $p$-values (Burnham and Anderson, 2004; Penny et al., 2004).
Results

Figure 2. Behavioural results, displayed across the entire control group (A, E, J) and for each lesion type separately together with their respective control participants (all other panels). Blue/L: low threat level. Purple/M: medium threat level. Orange/H: high threat level. Solid lines: control participants. Dashed lines: patients. MTL: surgical medial temporal lobe lesion. HC: selective bilateral hippocampus lesion. Amy: selective bilateral amygdala lesion. Approach and return are not displayed for the 6th token (potential loss 5 tokens) as this was rarely collected and therefore not included into statistical analysis.

Healthy control participants' behaviour is similar to previous reports

We first ensured that behaviour of control participants was comparable to previous reports (Bach, 2015, 2017; Khemka et al., 2017). In particular, action, approach latency, and return latency, all depended on threat level and potential loss in a linear manner (figure 2AE, table 2).
Table 2: Linear mixed effects model statistics from the combined control group (n = 43). For all outcome measures, the table shows Satterthwaite approximation to degrees of freedom. For action, p-values are based on further Greenhouse-Geisser correction to degrees of freedom using the epsilon value shown.

| Action (proportion approach) | Approach latency | Return latency |
|-------------------------------|------------------|----------------|
| **F df epsilon p** | **F df p** | **F df p** |
| Threat level                  | 32.48 2.0714 0.0028 <.001 | 42.06 2.0130 0.031 22.75 2.067059 <.001 |
| Threat level: linear          | 62.17 1.0714 0.001 | 46.07 1.0130 0.001 35.11 1.067059 <.001 |
| Potential loss                | 1994.83 4.0714 0.001 | 5.57 4.0130 0.001 22.38 4.067059 <.001 |
| Potential loss: linear        | 9406.32 1.0714 0.001 | 11.0 1.0130 0.001 31.11 1.067059 <.001 |
| Interaction threat level x potential loss | 5.86 8.0714 0.2047 0.006 2.42 8.0130 0.013 1.34 8.067059 .22 |
| Interaction linear x potential loss | 1.85 1.0714 0.17 | 6.46 1.0130 0.011 0.1 1.067059 .76 |

Recollection of threat memory

The association between colour and threat level depended on behaviour and had to be implicitly learned during the test. The control group learned this association successfully although not precisely: ratings of catch probability strongly depended on threat level (ANOVA: F(2, 84) = 68.6; p < .001) and on true catch rate (LME: F(1, 127) = 38.4; p < .001) (figure 3A). The relation between variations in true and estimated catch rate was close to perfect (regression coefficient b = 0.99), but there was a significant intercept (F(1, 127) = 115.8; p < .001): participants estimated catch rate 36.3% higher than the true catch rate. Comparing MTL lesion patients with their control group in an ANOVA with threat level as within-subjects factor, patients rated the catch probabilities as higher than the control group (63.7% vs. 51.4%, F(1, 11) = 5.0; p = .046). However, this was largely explained by higher true catch rates in patients. In a LME model accounting for true catch rates, there was no difference between the two groups for the intercept (F(1, 35) = 1.2; p = .28) or the regression coefficient (F(1, 35) = 1.2; p = .28).

Nevertheless, because of the known role of HC in declarative memory, we focused in our analysis on overall group differences, and on the impact of potential loss, rather than the
impact of threat level, on behaviour. Furthermore, we controlled for overall estimated
catch rate as a covariate in further analyses.

Figure 3. Explicit memory of catch rate after the experiment. True catch rate depends on behaviour and
may change over the course of the experiment. For lesion patients, colour/threat association was
randomised, and each control participant was presented with the same association as their respective
patient. Blue: low threat level. Purple: medium threat level. Orange: high threat level.

HC but not amygdala lesions impact on approach decision

Next, we tested our hypothesis that patients with MTL lesions would be more likely than
control participants to approach as potential loss increased. As expected, the linear
relation of potential loss with the proportion of approach differed between MTL lesions
and control individuals (figure 2B, table 3). This result was confirmed in a post-hoc test
of fitted linear coefficients (one-tailed t(11) = 1.98, p = 0.037) which are depicted in
figure 4A. The difference between patients with MTL lesions and controls was not better
explained by accounting for overall estimate of catch probability, years of education, or
visual memory (Rey-Osterrieth Complex Figure test).
Table 3: Parametric comparison of MTL lesion patients (n = 3) and control subjects (n = 10). Group:
patients/controls. Main effects and interactions not pertaining to group differences are omitted from the
table. For all outcome measures, the table shows Satterthwaite approximation to degrees of freedom. For
action, p-values are based on further Greenhouse-Geisser correction to degrees of freedom using the
epsilon value shown.

* p < .05 (shown in bold type)

| Action (proportion approach) | Approach latency | Return latency |
|-----------------------------|------------------|---------------|
| F                           | df               | oplum         | p   | F   | df | p   | F   | df | p   |< .001*|
| Group                       | 1                | 187           | 0.319| 2.20| 1  | 12577.6| 0.133| 19.04| 1 | 10061.1|
| Group x threat              |                  |               |      |     |    |       |      |     |    |       |
| level                       | 3.5              | 2              | 187  | 0.9762 | 0.033*| 1.32  | 2  | 12577.6| 0.267  | 0.21  | 2 | 10061.1| 0.815 |
| Group x potential           |                  |               |      |     |    |       |      |     |    |       |
| level: linear               | 0.17             | 1              | 187  | 0.683  | 0.56  | 1    | 12577.6| 0.453  | 0.34  | 1 | 10061.1| 0.562 |
| Group x potential           |                  |               |      |     |    |       |      |     |    |       |
| loss                        | 2.23             | 4              | 187  | 0.4751 | 0.135  | 1.19   | 4  | 12577.6| 0.313  | 0.47  | 4 | 10061.1| 0.755 |
| Group x potential           |                  |               |      |     |    |       |      |     |    |       |
| loss: linear                | 6.57             | 1              | 187  | 0.011* | 2.16   | 1    | 12577.6| 0.142  | 0.29  | 1 | 10061.1| 0.589 |

Interaction Group

| s threat level x               | potential loss | 1.49             | 8    | 187  | 0.2408 | 0.2391 | 0.40  | 8  | 12577.6| 0.871  | 0.58  | 8 | 10061.1| 0.798 |
| Interaction Group             | s linear x linear| 5.34             | 1    | 187  | 0.022  | 0.52   | 1    | 12577.6| 0.47   | 0.2   | 1 | 10061.1| 0.655 |

Next, we compared the impact of selective HC (figure 2C) or amygdala lesions (figure 2D) with the unselective MTL lesions, using an ordinal dissociation test. This test allows
a statement whether the observed rank difference between two patients is larger than
the rank difference between random pairs of control subjects. As visible in figure 4B, 2
out of 3 MTL patients as well as the selective HC patient had less negative linear
coefficients than all their respective controls. Indeed, the impairment of the HC patient
was even slightly more pronounced than the MTL lesion group (ordinal dissociation
test: p = .062). In contrast, the amygdala patient did not differ from its control group and
ranked at the 30th percentile, which was significantly different from the MTL patients
(ordinal dissociation test: p = .010) and from the selective HC lesion patient (ordinal
dissociation test: p = .001). Collectively, these results suggest that the decision to
approach is impaired due to hippocampus, but not due to amygdala, lesions.
Figure 4. A: Fitted linear coefficients for the relationship between potential loss and proportion of approach, for the control and MTL lesion group (mean ± pooled SEM). B-D: Fitted linear coefficients (B), mean approach latency (C), and mean return latency (D), for individual MTL patients (M1-M3), selective bilateral hippocampus lesion patient (HC), and selective bilateral amygdala lesion patient (Amy). Red dots: patients. *: p < .05 one-tailed

We also found an impact of MTL lesion on the relation between threat level and approach decision (table 3). Because the MTL and control group differed in the subjective estimation of catch rate, we replicated this result in a model with subjective catch probability as a linear predictor, as opposed to categorical threat level (F(1, 207.9) = 9.18, p = .003). Further investigating this latter result, we extracted the linear coefficient of the relation between catch probability and approach rate. For this coefficient, selective HC and amygdala patients had a non-significantly less pronounced deficit than the MTL patients (percent ranks: MTL 84%, HC 55%, amygdala 50%, MTL vs. HC: p = .077, MTL vs. amygdala: p = .057). This suggests that the deficit may be due to lesions outside HC/amygdala.
Selective HC and amygdala but not MTL lesions may impact on approach latency

We then analysed approach latency on those trials on which participants did approach the token (figure 2F). There was no significant difference between MTL lesion patients and the control group, such that we did not plan comparisons of MTL lesion with selective lesions. Descriptively, however, HC and amygdala patients differed from their control groups in that they approached faster overall (figure 2GH, figure 4C).

Exploratory analysis revealed that the HC patient (ordinal dissociation test: p = .010) and the amygdala patient (ordinal dissociation test: p = .016) approached faster than the MTL patients. There was no significant difference between HC and amygdala patients.

Amygdala/MTL but not selective HC lesions impact on return latency

We then analysed return latency on those trials on which participants successfully approached without getting caught (figure 2K), where our hypothesis was a deficit in return would be not be caused by HC lesions. Across all conditions, MTL patients returned to safety more slowly than controls (table 3). This difference between MTL patients and controls was not better explained by accounting for subjective catch rate, years of education, or visual memory. There were no other significant differences between MTL patients and controls. We then tested our hypothesis that this effect was specific to amygdala lesions, and compared MTL patients with selective HC and amygdala lesions (figure 2LM). As can be seen in figure 4D, MTL patients returned more slowly than any of their control subjects, while in contrast, HC patient was faster than 56% of its control subjects (ordinal dissociation test: p = .024). Thus, it appears that the observed deficit in return to safety is specific to extensive MTL lesions and does not occur in selective HC lesions. In contrast, amygdala lesion patient was slower than 90% of the control group and was not significantly different from the MTL patients. Taking
together all patients with unspecific MTL or amygdala lesions, they dissociated from
selective HC lesion patient (ordinal dissociation test: p < .011). This suggests that the
selective amygdala lesion patient was impaired in return to safety, just like MTL lesion
patients, but different from the selective HC lesion patient.

MTL lesions impact on response generation but not on subjective task structure

Figure 5. AB: Exposure times from the safe-predator-exposure task for MTL lesion controls (A) and MTL
lesion patients (B), with respect to the most recently appearing token. % responses: Percentage of
responses included in the plot; remaining responses were made before the first token occurred. Red lines
show the expected exposure times under a uniform null distribution across the trial. C: Evidence for
different models to distinguish controls and MTL patients expressed as log Bayes Factors (LBF, larger is
better) with respect to a reference model with no difference between the group (combined). Dashed line
indicates decisiveness threshold (LBF difference > 3).

Finally, we sought to disambiguate possible causes for behavioural alterations in
MTL/HC patients. We have previously demonstrated in this task that healthy people
behave consistent with a subjective prior assumption that the occurrence of tokens
alerts the predator. They were asked in a separate part of the game to indicate when
they thought the predator was awake, and instructed they would be rewarded for
exposing the predator when it was indeed awake. Healthy participants predominantly
guessed that the predator was awake immediately after an (irrelevant) token appeared
on the screen, despite explicit instructions that tokens were irrelevant to the task,
despite feedback that such relation did not exist in the task and although this behaviour
made the experiment last longer. Crucially, while token collection behaviour changes
after negative consequences, this was hardly the case for predator exposure behaviour in our previous report (Bach, 2017). The same pattern was observed in the current control group (figure 5A, KS-test, p < .001). The distribution of exposure times differed between each MTL or HC lesion patients and its respective control subjects (KS-test, p < .001). However, there was no consistent difference between controls and MTL lesion patients regarding the mean exposure time in a t-test. We then fit a previously validated model to the distribution of exposure times, in which exposure times are a weighted sum of a process that distributes responses evenly across a trial, and a second process that implements a simple response to the token and is modelled by an exGauss distribution. We fit a model with the same parameters for patients and controls (combined model, figure 5C), as well as several models that split up either the exGauss parameters mu or lambda, or the weighting parameter w, or lambda and w, between patients and controls. For the group of MTL patients and their respective control participants, the best fit was achieved when splitting up the parameter lambda and not the other parameters (figure 5C, log Bayes Factor difference between best and second best model: 3.6). This parameter governs the decay of the simple response process and is unrelated to prior assumptions about token-predator correlations. The same winning model but with a less decisive Log Bayes Factor was found for the selective HC patient lesion patients markedly differed in their response distributions from control participants, we found no evidence that this was due to different subjective priors about the structure of the task.
In this paper, we sought to disentangle the contribution of hippocampus and amygdala to individual actions in a human approach/avoidance conflict test. We found that HC but not amygdala lesions impacted on the decision to approach reward under threat when potential loss was high. In contrast, in amygdala but not HC lesions we observed reduced return vigour after approaching threat. Additionally, unspecific MTL lesion patients but not specific HC or amygdala lesion patients were impaired in adjusting their approach rate to threat level. As an exploratory result, an alteration in behavioural inhibition was only observed in the selective HC and amygdala lesion patients. We note that this was not a planned analysis. Finally, we did not find evidence that HC lesions alter the subjective representation of threat/reward correlations, something that we have proposed to underlie approach delay in healthy individuals (Bach, 2015, 2017).

Regarding the impact of HC lesions, our current finding is in keeping with a previous result in a spatially extended human approach/avoidance task. Here, patients with degenerative HC lesions were more often outside a safe place when potential loss was high (Bach et al., 2014b). However, in this setup it was difficult to separate threat approach from other actions including return to safety. Our current findings suggest that the impairment previously observed in HC lesion patients is due to increased threat approach under conflict. At the same time, amygdala lesion patient BG who showed the same deficit as HC lesion patients in this previous task (Korn et al., 2017) was in the current task not impaired in decision to approach, but instead in return to safety, an important component of our previous task as well. This underlines the necessity to separate action components to delineate the contribution of different brain structures.
While hippocampus is traditionally investigated in the context of spatial navigation, cognitive maps, and declarative memory, another important aspect is its role in anxiety-like behaviour (Calhoun and Tye, 2015). The current approach of separating action components may help to reconcile these views, by allowing a more specific inference on the type of approach/avoidance conflict behaviour on which hippocampus lesions impact. For example, our current results are not predicted by a view according to which HC represents threat/reward aspects of a situation. In this case, one would have expected an alteration in approach latency and return vigour as well, since all action components in the task empirically depend on threat level and potential loss. Instead, our findings may tentatively suggest that hippocampus is specifically involved in a decision to approach under conflict, as initially suggested by (Gray and McNaughton, 2000). We note that because of the known role of hippocampus for learning and memory, our interpretation hinges on the assumption that lesion patients learned the task structure to the same extent as control participants. Crucially, MTL and hippocampus lesion patients showed a behavioural alteration only when token loss was high (3-5 tokens) but they behaved similarly to control participants when loss was low (0-2 tokens), i.e. showed the same reduction of approach rate with potential loss. Understanding the task structure is important at lower token loss, and it appears unlikely to observe this behaviour if patients had not learned the task structure.

Previous non-human primate work pitting food reward against innate threat stimuli (rubber snakes) has revealed increased approach behaviour after HC lesions, in line with the current study. Different from our study, however, they also observed reduced defensive behaviour after HC lesions (Chudasama et al., 2008; Chudasama et al., 2009).
In their test, the conflict situation lasted for 30 seconds and there was no incentive to act rapidly. To reconcile this with our findings, it is possible that in addition to approach decisions, HC is also involved in certain types of defensive behaviours, but excluding the rapid withdrawal behaviour required in our study. As a crucial factor for involvement of HC as well as for the type of behaviour elicited, defensive distance has been suggested (Fanselow and Lester, 1988; Gray and McNaughton, 2000; Blanchard et al., 2011). In contrast, the reduction in approach latency that our exploratory analysis suggested in both types of selective lesions may not be specific to approach/avoidance conflict: similar reduction in response times after HC lesions has also been observed in purely reward-related rodent tasks (Schwarting and Busse, 2017).

Impairment in return vigour after amygdala lesions is consistent with a rodent literature investigating non-conflict active avoidance (LeDoux et al., 2017; Terburg et al., 2018). Return to safety is a crucial component of many ethological approach/avoidance conflict tests, including our previous human version. It remains to be shown how this relates to the inconsistent reports of an amygdala role in various approach/avoidance conflict tests (Kirlic et al., 2017). Furthermore, recent work has highlighted how subregions within amygdala regulate approach towards, or avoidance of, threat in the absence of explicit or putative reward (Miller et al., 2019).

As a side finding, only unspecific MTL lesion patients were impaired in adjusting their approach rate to threat level. Although evidence for dissociation between MTL and selective lesions was not significant, one may speculate that this deficit is due to lesions outside HC or amygdala. Furthermore, different from the other findings, it may be explained by impairment in learning colour-threat level association sufficiently.
As a limitation, our human lesion approach is agnostic to the contribution of HC and amygdala subregions, or microcircuitry on the level of transmitter systems. For example, anterior CA1 and CA3 appear to intricately balance their contributions to approach/avoidance conflict behaviour such that specific lesions have opposing effects (Schumacher et al., 2018). Also, lesions specific to the serotonergic system within amygdala may have effects that depend on the type of conflict test (Sommer et al., 2001). For another example, anterior hippocampus inactivation had no impact on approach behaviour in a specific approach/avoidance task in marmosets, while increasing glutamine levels did (Wallis et al., 2019). Furthermore, a growing body of evidence suggests a longitudinal axis specialisation of the hippocampus, with dorsal parts contributing more to spatial navigation and memory, and ventral parts more to anxiety tests (Strange et al., 2014). There appears to be no clear distinction between different hippocampal regions, but rather a gradient of functional contribution to different tasks.

Such subtle distinctions cannot be made in clinical lesion model employed here. Nevertheless, by investigating more and diverse lesion types within MTL, it may be possible to ultimately triangulate the specific function of anatomical or functional subdivisions. Furthermore, back-translating our approach of separating action components to rodents (Oberrauch et al. 2019) and non-human primates may help to provide a clearer picture of cross-species differences.

Ultimately, finer conceptual granularity may also help translate results from approach/avoidance conflict tests into clinical questions. Indeed, decades of research on these tests have had relatively little impact on etiological concepts or treatment of anxiety disorders (Stephan et al., 2016). It appears that different action components in
approach/avoidance conflict tests resemble symptoms of different disorders. In this context, we note that an important behavioural component that was not investigated in the current setup is the duration of a decision, which may be relevant to rumination and worry in generalised anxiety disorder (Craske et al., 2017), for which approach/avoidance tests are often seen as a preclinical model (Calhoon and Tye, 2015).

This can be investigated in tests that extend approach/avoidance conflict over time with no incentive to act quickly, such that approach latency has a different meaning than in our task (Chudasama et al., 2008; Chudasama et al., 2009).

We have previously demonstrated a linear relation of threat level with HC gamma oscillations (Khemka et al., 2017) and - biophysically related - BOLD signal (Bach et al., 2014b; Korn and Bach, 2019) in several different human approach/avoidance tasks. In the current task, we did not observe any lesion-induced change in the linear relation of threat level with behaviour. Future work will investigate how these neuroimaging findings can be reconciled with the pattern of lesion impairment.

To summarise, our findings add to the growing evidence that implicates the human hippocampal formation in a surprising variety of non-mnemonic behaviors such as decision-making, creativity, and prospective planning. It will be important to scrutinize how the observed deficits translate into real-world behavior in clinical populations.
Acknowledgements

The authors thank Rosa Bohlender and Dirk Scheele for help with data collection, and Samuel Gerster for technical support. This work was partly funded by Deutsche Forschungsgemeinschaft (DFG, German Research Foundation, B05 – SFB 1315). The Wellcome Centre for Human Neuroimaging is supported by the Wellcome Trust [091593/Z/10/Z].
References

Amemori K, Amemori S, Graybiel AM (2015) Motivation and affective judgments differentially recruit neurons in the primate dorsolateral prefrontal and anterior cingulate cortex. J Neurosci 35:1939–1953.

Bach DR (2015) Anxiety-Like Behavioural Inhibition Is Normative under Environmental Threat-Reward Correlations. PLoS computational biology 11:e1004646.

Bach DR (2017) The cognitive architecture of anxiety-like behavioral inhibition. J Exp Psychol Hum Percept Perform 43:18–29.

Bach DR, Hurlemann R, Dolan RJ (2013) Unimpaired discrimination of fearful prosody after amygdala lesion. Neuropsychologia 51:2070–2074.

Bach DR, Hurlemann R, Dolan RJ (2014a) Impaired threat prioritisation after selective bilateral amygdala lesions. Cortex; a journal devoted to the study of the nervous system and behavior 63C:206-213.

Bach DR, Korn CW, Vunder J, Bantel A (2018) Effect of valproate and pregabalin on human anxiety-like behaviour in a randomised controlled trial. Transl Psychiatry 8:157.

Bach DR, Talmi D, Hurlemann R, Patin A, Dolan RJ (2011) Automatic relevance detection in the absence of a functional amygdala. Neuropsychologia 49:1302–1305.

Bach DR, Guitart-Masip M, Packard PA, Miro J, Falip M, Fuentemilla L, Dolan RJ (2014b) Human Hippocampus Arbitrates Approach-Avoidance Conflict. Current Biology 24:541-547.

Bannerman DM, Sprengel R, Sanderson DJ, McHugh SB, Rawlins JN, Monyer H, Seeburg PH (2014) Hippocampal synaptic plasticity, spatial memory and anxiety. Nat Rev Neurosci 15:181-192.

Becker B, Mihov Y, Scheele D, Kendrick KM, Feinstein JS, Matusch A, Aydin M, Reich H, Urbach H, Oros-Peusquens AM, Shah NJ, Kunz WS, Schlaepfer TE, Zilles K, Maier W, Hurlemann R (2012) Fear processing and social networking in the absence of a functional amygdala. Biological psychiatry 72:70-77.

Blanchard DC, Griebel G, Pobbe R, Blanchard RJ (2011) Risk assessment as an evolved threat detection and analysis process. Neuroscience and biobehavioral reviews 35:991-998.

Braun M, Finke C, Ostendorf F, Lehmann TN, Hoffmann KT, Ploner CJ (2008) Reorganization of associative memory in humans with long-standing hippocampal damage. Brain 131:2742-2750.

Britton DR, Britton KT (1981) A Sensitive Open-Field Measure of Anxiolytic Drug Activity. Pharmacol Biochem Be 15:577-582.

Burnham KP, Anderson DR (2004) Multimodel inference - understanding AIC and BIC in model selection. Sociol Method Res 33:261-304.

Calhoon GG, Tye KM (2015) Resolving the neural circuits of anxiety. Nat Neurosci 18:1394-1404.

Chudasama Y, Wright KS, Murray EA (2008) Hippocampal lesions in rhesus monkeys disrupt emotional responses but not reinforcer devaluation effects. Biological psychiatry 63:1084-1091.

Chudasama Y, Izquierdo A, Murray EA (2009) Distinct contributions of the amygdala and hippocampus to fear expression. Eur J Neurosci 30:2327-2337.

Craske MG, Stein MB, Eley TC, Milad MR, Holmes A, Rapee RM, Wittchen HU (2017) Anxiety disorders. Nat Rev Dis Primers 3:17024.

31
Crawford JR, Garthwaite PH (2005a) Testing for suspected impairments and
dissociations in single-case studies in neuropsychology: evaluation of
alternatives using monte carlo simulations and revised tests for dissociations.
Neuropsychology 19:318-331.
Crawford JR, Garthwaite PH (2005b) Evaluation of criteria for classical dissociations in
single-case studies by Monte Carlo simulation. Neuropsychology 19:664-678.
Crawford JR, Howell DC, Garthwaite PH (1998) Payne and Jones revisited: estimating the
abnormality of test score differences using a modified paired samples t test. J Clin
Exp Neuropsychol 20:898-905.
Crawford JR, Garthwaite PH, Gray CD (2003) Wanted: fully operational definitions of
dissociations in single-case studies. Cortex; a journal devoted to the study of the
nervous system and behavior 39:357-370.
Esfahani-Bayerl N, Finke C, Kopp U, Moon D-U, Ploner CJ (2019) Musical memory and
hippocampus revisited: Evidence from a musical layperson with highly selective
hippocampal damage. Cortex; a journal devoted to the study of the nervous
system and behavior in press.
Esfahani-Bayerl N, Finke C, Braun M, Duzel E, Heekeren HR, Holtkamp M, Hasper D,
Storm C, Ploner CJ (2016) Visuo-spatial memory deficits following medial
temporal lobe damage: A comparison of three patient groups. Neuropsychologia
81:168-179.
Evans DA, Stempel AV, Vale R, Ruehle S, Lefler Y, Branco T (2018) A synaptic threshold
mechanism for computing escape decisions. Nature 558:590-594.
Fanselow MS, Lester LS (1988) A functional behavioristic approach to aversively
motivated behavior: Predatory imminence as a determinant of the topography of
defensive behavior.
Finke C, Braun M, Ostendorf F, Lehmann TN, Hoffmann KT, Kopp U, Ploner CJ (2008) The
human hippocampal formation mediates short-term memory of colour-location
associations. Neuropsychologia 46:614-623.
Geller I, Seifert J (1960) A Conflict Procedure for the Evaluation of Drugs. Fed Proc
19:20-20.
Gray JA, McNaughton N (2000) The neuropsychology of anxiety: An enquiry into the
functions of the septohippocampal system. Oxford, UK: Oxford University Press.
Hurlemann R, Wagner M, Hawellek B, Reich H, Pieperhoff P, Amunts K, Oros-Peusquens
AM, Shah NJ, Maier W, Dolan RJ (2007) Amygdala control of emotion-induced
forgetting and remembering: evidence from Urbach-Wiethe disease.
Neuropsychologia 45:877-884.
Ito R, Lee ACH (2016) The role of the hippocampus in approach-avoidance conflict
decision-making: Evidence from rodent and human studies. Behavioural Brain
Research 313:345-357.
Khemka S, Barnes G, Dolan RJ, Bach DR (2017) Dissecting the Function of Hippocampal
Oscillations in a Human Anxiety Model. J Neurosci 37:6869-6876.
Kirlc N, Young J, Aupperle RL (2017) Animal to human translational paradigms relevant
for approach avoidance conflict decision making. Behav Res Ther 96:14-29.
Korn CW, Bach DR (2019) Minimizing threat via heuristic and optimal policies recruits
hippocampus and medial prefrontal cortex. Nat Hum Behav.
Korn CW, Vunder J, Miro J, Fuentemilla L, Hurlemann R, Bach DR (2017) Amygdala
Lesions Reduce Anxiety-like Behavior in a Human Benzodiazepine-Sensitive
Approach-Avoidance Conflict Test. Biological psychiatry 82:522-531.
LeDoux JE, Moscarello J, Sears R, Campese V (2017) The birth, death and resurrection of avoidance: a reconceptualization of a troubled paradigm. Molecular psychiatry 22:24-36.

Luke SG (2017) Evaluating significance in linear mixed-effects models in R. Behav Res Methods 49:1494-1502.

Miller SM, Marcotulli D, Shen A, Zweifel LS (2019) Divergent medial amygdala projections regulate approach-avoidance conflict behavior. Nat Neurosci 22:565-575.

Montgomery KC (1955) The Relation between Fear Induced by Novel Stimulation and Exploratory Behavior. J Comp Physiol Psych 48:254-260.

Pellow S, Chopin P, File SE, Briley M (1985) Validation of Open - Closed Arm Entries in an Elevated Plus-Maze as a Measure of Anxiety in the Rat. J Neurosci Meth 14:149-167.

Penny WD, Stephan KE, Mechelli A, Friston KJ (2004) Comparing dynamic causal models. NeuroImage 22:1157-1172.

Raftery AE (1995) Bayesian model selection in social research. Sociol Methodol 25:111-163.

Rempel-Clower NI, Zola SM, Squire LR, Amaral DG (1996) Three cases of enduring memory impairment after bilateral damage limited to the hippocampal formation. J Neurosci 16:5233-5255.

Rodgers RJ, Cao BJ, Dalvi A, Holmes A (1997) Animal models of anxiety: an ethological perspective. Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas / Sociedade Brasileira de Biofisica [et al] 30:289-304.

Schumacher A, Villaruel FR, Usling A, Riaz S, Lee ACH, Ito R (2018) Ventral Hippocampal CA1 and CA3 Differentially Mediate Learned Approach-Avoidance Conflict Processing. Current biology : CB 28:1318-1324 e1314.

Schwarting RK, Busse S (2017) Behavioral facilitation after hippocampal lesion: A review. Behav Brain Res 317:401-414.

Shin MS, Park SY, Park SR, Seol SH, Kwon JS (2006) Clinical and empirical applications of the Rey-Osterrieth Complex Figure Test. Nat Protoc 1:892-899.

Somer W, Moller C, Wiklund L, Thorsell A, Rimondini R, Nissbrandt H, Heilig M (2001) Local 5,7-dihydroxytryptamine lesions of rat amygdala: release of punished drinking, unaffected plus-maze behavior and ethanol consumption. Neuropsychopharmacology 24:430-440.

Stephan KE, Bach DR, Fletcher PC, Flint J, Frank MJ, Friston KJ, Heinz A, Huys QJ, Owen MJ, Binder EB, Dayan P, Johnstone EC, Meyer-Lindenberg A, Montague PR, Schnyder U, Wang XJ, Breakspear M (2016) Charting the landscape of priority problems in psychiatry, part 1: classification and diagnosis. Lancet Psychiatry 3:77-83.

Strange BA, Witter MP, Lein ES, Moser EI (2014) Functional organization of the hippocampal longitudinal axis. Nat Rev Neurosci 15:655-669.

Talmi D, Hurlemann R, Patin A, Dolan RJ (2010) Framing effect following bilateral amygdala lesion. Neuropsychologia 48:1823-1827.

Terburg D, Scheggi D, Triana Del Rio R, Klumpers F, Ciobanu AC, Morgan B, Montoya ER, Bos PA, Giobellina G, van den Burg EH, de Gelder B, Stein DJ, Stoop R, van Honk J (2018) The Basolateral Amygdala Is Essential for Rapid Escape: A Human and Rodent Study. Cell 175:723-735 e716.

Vogel JR, Beer B, Clody DE (1971) Simple and Reliable Conflict Procedure for Testing Anti-Anxiety Agents. Psychopharmacologia 21:1-&.
Wallis CU, Cockcroft GJ, Cardinal RN, Roberts AC, Clarke HF (2019) Hippocampal Interaction With Area 25, but not Area 32, Regulates Marmoset Approach-Avoidance Behavior. Cereb Cortex.