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Optimising a model-based approach to inferring fear learning from skin conductance responses

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HIGHLIGHTS

- We validate a Psychophysiological model (PsPM) to infer anticipatory sympathetic arousal from changes in skin conductance.
- We optimise the inversion of this PsPM in terms of a constrained non-linear dynamic causal model.
- This method allows a quantification of fear memory in humans.

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ABSTRACT

Anticipatory sympathetic arousal is often inferred from skin conductance responses (SCR) and used to quantify fear learning. We have previously provided a model-based approach for this inference, based on a quantitative Psychophysiological Model (PsPM) formulated in non-linear dynamic equations. Here we seek to optimise the inversion of this PsPM. Using two independent fear conditioning datasets, we benchmark predictive validity as the sensitivity to separate the likely presence or absence of the unconditioned stimulus. Predictive validity is optimised across both datasets by (a) using a canonical form of the SCR shape (b) filtering the signal with a bi-directional band-pass filter with cut off frequencies 0.0159 and 5 Hz, (c) simultaneously inverting two trials (d) explicitly modelling skin conductance level changes between trials (e) the choice of the inversion algorithm (f) *z*-scoring estimates of anticipatory sympathetic arousal from each participant across trials. The original model-based method has higher predictive validity than conventional peak-scoring or an alternative model-based method (Ledalab), and benefits from constraining the model, optimised data preconditioning, and post-processing of ensuing parameters.

1. Introduction

Central states of sympathetic arousal (SA) are often inferred from skin conductance responses (SCR), for example to quantify associative learning in the context of fear conditioning (Morris and Dolan, 2004; Delgado et al., 2006; Boucsein, 2012). This inference relies on assumptions of how SA and SCR relate to each other. Psychophysiological Models (PsPM) explicitly describe how sudomotor nerve activity generates observable SCR (a peripheral model), and constrain at what points in time sudomotor nerve activity can be generated by experimentally induced SA (a neural model) (Bach and Friston, 2013). The combined forward model SA$\longmapsto$SCR can be turned backwards, to arrive at the relation SA$\longleftarrow$SCR. In statistics, this process is often termed "model inversion", and it provides probabilistic estimates of the most likely SA, given SCR. Model-based estimates of SA are more sensitive than estimates from conventional analysis techniques such as SCR peak scoring, as we have shown in previous theoretical (Bach and Friston, 2013) and empirical work (Bach et al., 2009, 2010a, 2011a; Bach, 2014). They are also more sensitive than model-based methods relying only on a peripheral model, without a constraining neural model (Benedek and Kaernbach, 2010; Bach, 2014).

Models for evoked SCR, generated by short experimental events with a known latency, have been developed, refined, and evaluated, in the framework of General Linear Convolution Modelling (GLM) (Bach et al., 2009, 2010b, 2013; Bach, 2014). Yet, one of the most common applications of SA/SCR is to quantify associative learning in fear conditioning. When a conditioned stimulus (CS+) is presented, sympathetic arousal occurs in preparation for the upcoming unconditioned stimulus (US) (Balleine and Killcross, 2006). Because

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the CS usually extends over time, the onset of preparatory SA is not known and may vary from trial to trial which precludes using linear inversion methods such as GLM. We have previously developed a model-based approach for estimating amplitude, onset, and duration of anticipatory SA (Bach et al., 2010a). This model is formulated in terms of non-linear dynamic equations, and inverted by a variational Bayes algorithm (VBA) developed in the framework of DCM (Daunizeau et al., 2009). Estimates from this method can better distinguish CS+ from CS− trials, compared to a GLM approach that assumes constant latency, and also compared to standard peak scoring.

As with any method, this approach involves certain technical choices that are beyond the known biophysical properties of the studied system. Here, we revisit some of these customisable settings with the aim of optimising the method. We compare (a) response functions for the peripheral model, (b) filter parameters applied to raw SCR data, (c) number of simultaneously inverted trials (d) inclusion of SCL, (e) inversion algorithms and (f) removing between subject variance from SA estimates.

We benchmark the sensitivity of our method by its ability to correctly infer known states of arousal in humans during fear learning. Because SA cannot be observed directly, we rely on the assumption that presentations of CS+ categorically elicit stronger SA than CS−, in a fear learning paradigm with many trials and CS that are easy to learn. We term the ability to differentiate neural states from CS+ and CS− predictive validity. For each set of SA estimates, we compute the negative log likelihood that SA estimates for CS− and CS+ trials are drawn from two different distributions rather than the same distribution, analogous to a paired *t*-test. We can then calculate the log Bayes factor as difference between negative log likelihood of the evaluated model against a reference model. In this context, lower log Bays factor implies higher predictive validity for the evaluated model. As reference model we used inversion with the current default settings. The algorithm evaluated here is available as part of the Matlab suite PsPM (incorporating SCRalyze) at http://pspm.sourceforge.net.

2. Material and methods

2.1. Design and data

2.1.1. General settings

We analysed data recorded from two independent experiments using a discriminant delay fear conditioning paradigm. Data from experiment (1) [HRA] are published (Bach et al., 2010a); data from experiment (2) [SCBD/SC1F] are yet unpublished. Trial order was pseudo-randomised. CSs were presented for 4 s, and a reinforced CS+ co-terminated with the US. Both experiments were programmed in Cogent 2000 (Version 1.25; www.vislab.ucl.ac.uk/Cogent) and run on Matlab 6.5 and 8.1, respectively.

In both experiments, 50% of the CS+ were reinforced with a train of electric square pulses (Experiment 1: 500 Hz, Experiment 2: 50 Hz) with individual square pulse width of 0.5 ms, delivered via a constant-current stimulator (Digitimer DS7A, Digitimer, Welwyn Garden City, UK) through a pin-cathode/ring-anode configuration at the dominant forearm. Before the experiment, shock intensity was set to a clearly uncomfortable level. First, electric current was increased from an undetectable intensity until the participant reported that stimulation was above the pain threshold. Then, shocks with a randomly set intensity below the maximum intensity were applied while the participant rated discomfort on a 0 (no shock detected) to 100 (painful) scale. Finally, the stimulation was set just below the pain threshold. This resulted in a current of 0.90 ± 0.63 mA (mean ± SD) for experiment 1 and 6.31 ± 8.20 mA for experiment 2. Skin conductance was recorded as described previously (Bach et al., 2009, 2010a) on thenar/hypothenar of the non-dominant hand using 8 mm Ag/AgCl cup electrodes (EL258, Biopac Systems Inc., Goleta, CA, USA) and 0.5%-NaCl electrode paste (GEL101; Biopac) (Hygge and Hugdahl, 1985). We recruited healthy unmedicated participants from the general population who received monetary compensation for their participation. All participants gave written informed consent, and the study protocols, including the form of consent, were approved by the competent research ethics committees.

2.1.2. Experiment 1

20 individuals between 18 and 30 years (10 female, mean age ± standard deviation: 22.2 ± 4.0 years) took part in experiment 1. CSs were a blue and an orange filled circle on a black background that were presented on each trial on the left or on the right of the screen centre. Participants were tasked to indicate the colour with the cursor up/cursor down key. Colour-key and colour-CS associations were balanced across participants. Inter-trial interval (ITI) was randomly drawn in each trial from 7, 8, 9, 10, or 11 s. At the end of 20 randomly selected trials (10 CS−, 5 CS+ with US, 5 CS+ without US), participants were asked to rate "'How likely did you think you would get a shock?" using a horizontal visual analogue scale (VAS) from 0% to 100%. There were 90 trials for each CS type in 4 blocks. The whole experiment lasted about 45 min. For SCR recordings, constant voltage (2.5 V) was provided by a custom-build coupler, whose output was converted to an optical pulse with a minimum frequency of 100 Hz to avoid aliasing, digitally converted (Micro1401, CED, Cambridge, UK), and recorded (Spike2, CED).

2.1.3. Experiment 2

30 individuals between 18 and 35 years (15 female, mean age ± standard deviation: 25.3 ± 4.1 years) participated in experiment 2. 20 data sets were recorded during a functional magnetic resonance imaging (fMRI) experiment, and 10 data sets were recorded outside the MRI environment. In both data sets, participants underwent fear learning with the same stimuli. CSs were computer generated sine sounds of either single frequency (type 1: CS1+, CS1−) or triads of three different frequencies with a minor and major mode (type 2: CS2+, CS2−). For type 1 sounds, participants were asked to indicate the pitch (high, low) in each trial and for type 2 sounds to choose the correct mode (minor, major) with the left/right keys using the dominant hand. For half of the participants, sounds from both types were in a low frequency range (110 to 218 Hz) and for the other participants sounds were in a high frequency range (245 to 494 Hz). In the fMRI data set there were 96 trials in 4 blocks, and in the remaining data sets 128 trials in 2 blocks, with the same number of single sine and triad sounds. Within each block, 50% of trials were CS+ and 50% CS−. Inter-trial interval (ITI) was randomly drawn in each trial from 7, 9, or 11 s. The experiment outside the fMRI scanner lasted about 35 min while the fMRI experiment included 4 additional control blocks with novel unreinforced sounds, summing up to 45 min. These control trials are not included in the present analysis. For SCR acquisition in the fMRI scanner, we recorded data at 1000 Hz sampling frequency with a Biopac MP150 data acquisition system coupled to a GSR-100 C signal amplifier (BIOPAC Systems, Inc. Camino Goleta, CA). Outside the scanner, data were recorded at 200 Hz sampling rate with an integrated SCR coupler/amplifier (LabLinc V71-23, Coulbourn) and AD converter (DI-149/Windaq, Dataq). Differences between the two experimental environments were tested in a two-way ANOVA of CS (CS+, CS−) and environment, indicating no interaction, $F(1,56) = 0.82$, $p > 0.05$. Thus, for all subsequent analyses, data from both environments were pooled. Temperature and relative humidity of the experimental chamber