

Psychiatrische Universitätsklinik Zürich

FEAR CONDITIONING

Comparison of Models in PsPM & New Methods

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Bachlab.o^{rc}

Fear Conditioning

- Fear conditioning
 - contribute to survival
 - CS US association



Fear Conditioning

- Fear conditioning
 - contribute to survival
 - CS US association



Fear Conditioning measures

- Skin Conductance Responses
- Pupil Size Responses
- Heart Period Responses
- Respiration Amplitude Responses
- Fear-Potentiated Startle Responses
- Limb Withdrawal Responses
- Gaze Direction Responses
- Reaction Time
- Pavlovian-to-Instrumental Transfer
- Explicit Report

[Ojala & Bach 2020]



Fear Conditioning measures in PsPM

- Skin Conductance Responses
- Pupil Size Responses
- Heart Period Responses
- Respiration Amplitude Responses
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- Limb Withdrawal Responses
- Gaze Direction Responses
- Reaction Time
- Pavlovian-to-Instrumental Transfer
- Explicit Report

[Ojala & Bach 2020]



CONTENTS

- Comparison of Models in PsPM
 - Skin Conductance Response
 - Pupil Size Response
 - Fear-Conditioned Bradycardia
 - Respiration Amplitude Responses
 - Fear-Potentiated Startle

- New Methods
 - Pavlovian-to-Instrumental Transfer
 - Scanpath Length / Speed

Fear Conditioning measures in PsPM – Skin Conductance Responses



Conditioned stimuli (CS) \rightarrow SA \rightarrow SCR

Fear Conditioning measures in PsPM – Skin Conductance Responses



- Canonical response function in a non-linear model ("DCM");
- Trial-by-trial
- Flexible latency after CS onset
- Experiments with short (up to 4 s) CS-US interval

Fear Conditioning measures in PsPM – Skin Conductance Responses

Exp 1:

20 participants; CSs: blue or orange filled circles; 3.5 s SOA; 50% reinforcement

Exp 2:

30 participants; CSs: sine sounds of different frequencies; 3.5 s SOA; 50% reinforcement

	Experiment 1			Experiment 2		
	CS+>CS-		Comparison with default DCM:	CS+>CS-		Comparison with default DCM:
	t(19)	р	LBF (smaller is better)	t(29)	р	LBF (smaller is better)
Default DCM	3.88	0.001		3.55	0.001	
Peak	1.99	0.062	18	2.32	0.027	11
CDA ('AmpSum')	2.39	0.027	15	2.77	0.010	08
CDA ('SCR')	2.56	0.019	13	2.64	0.013	09
DCM (z-standard)	4.31	< 0.001	-2	3.64	0.001	-1
Peak (z-standard)	2.12	0.047	17	2.64	0.013	09
CDA ('AmpSum') (z-standard)	2.59	0.018	13	2.95	0.006	06
CDA ('SCR') (z-standard)	2.92	0.009	10	2.94	0.006	06

Fear Conditioning measures in PsPM – Skin Conductance Responses

	Experiment 1			Experime	Experiment 2		
	CS+>CS-		Comparison with default DCM:	CS+>CS-		Comparison with default DCM:	
	t(19)	р	LBF (smaller is better)	t(29)	р	LBF (smaller is better)	
Default DCM Peak CDA ('AmpSum') CDA ('SCR')	3.88 1.99 2.39 2.56	0.001 0.062 0.027 0.019	18 15 13	3.55 2.32 2.77 2.64	0.001 0.027 0.010 0.013	11 08 09	
DCM (z-standard) Peak (z-standard) CDA ('AmpSum') (z-standard) CDA ('SCR') (z-standard)	4.31 2.12 2.59 2.92	<0.001 0.047 0.018 0.009	-2 17 13 10	3.64 2.64 2.95 2.94	0.001 0.013 0.006 0.006	-1 09 06 06	

	Weighted average effect size (Cohen's d)
Peak scoring	0.44
PsPM	0.75

Fear Conditioning measures in PsPM – Skin Conductance Responses



To investigate a placebo-controlled fear memory intervention with at least 80% power at α = .05 in a one-tailed test, under the assumption of equal variance in control and intervention groups (best-case scenario) with a fear memory reduction of at least 50%

Fear Conditioning measures in PsPM – Skin Conductance Responses



	Cohen's d	Sample size
Peak scoring	0.44	514
PsPM	0.75	174

Fear Conditioning measures in PsPM – Skin Conductance Responses

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Fear Conditioning measures in PsPM – Pupil Size Responses



Conditioned stimuli (CS) \rightarrow cognitive inputs \rightarrow PSR

[Korn et al. 2017] 14

Fear Conditioning measures in PsPM – Pupil Size Responses



- Exp 1: 19 participants; Auditory CSs; 3.5 s SOA; 50% reinforcement
- Exp 2: 12 participants; Auditory CSs; 3.5 s SOA; 50% reinforcement
- Exp 3: 17 participants; Visual CSs; 3.5 s SOA; 50% reinforcement
- Exp 4: 18 participants; Somatosensory CSs; 3.5 s SOA; 50% reinforcement
- Exp 5: 15 participants; Long auditory CSs; 6 s SOA; 50% reinforcement [Korn et al. 2017]

Fear Conditioning measures in PsPM – Pupil Size Responses



- A gamma probability density function in a General linear model (GLM)
- Trial-by-trial
- CS-locked
- Experiments with different CS types, and luminance changes

Fear Conditioning measures in PsPM – Pupil Size Responses

Table	3.	Mode!	Comparison
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		t, p, and d values			
Experiment	Peak amplitude	AUC	GLM with response function from Experiment 1	GLM with response function from Experiment 1 plus derivative	
Experiment 1: Auditory CS $(n = 19)$	t(18) = 4.41; p = .0003; d = 1.01	t(18) = 3.97; p = .0009; d = 0.91	t(18) = 5.05; $p < 10^{-4};$ d = 1.16	t(18) = 5.89; $p < 10^{-4};$ d = 1.35	
Experiment 2: Auditory CS $(n = 12)$	t(11) = 2.63; p = .0234; d = 0.76	t(11) = 3.29; p = .0073; d = 0.95	t(11) = 3.09; p = .0104; d = 0.89	t(11) = 2.10; p = .0593; d = 0.61	
Experiment 3: Visual CS (n = 17)	t(16) = 2.71; p = .0155; d = 0.66	t(16) = 2.20; p = .0432; d = 0.53	t(16) = 2.96; p = .0093; d = 0.72	t(16) = 2.91; p = .0103; d = 0.71	
Experiment 4: Somatosensory CS $(n = 18)$	t(17) = 2.46; p = .0248; d = 0.58	t(17) = 2.53; p = .0216; d = 0.60	t(17) = 3.16; p = .0058; d = 0.74	t(17) = 2.87; p = .0107; d = 0.68	
Experiment 5: Long auditory CS $(n = 15)$	t(14) = 1.62; p = .1271; d = 0.42	t(14) = 2.43; p = .0289; d = 0.63	t(14) = 3.76; p = .0021; d = 0.97	t(14) = 3.78; p = .0020; d = 0.98	

	Weighted average effect size (Cohen's d)
Peak scoring	0.60
PsPM	0.82

[Korn et al. 2017; Bach & Melinscak 2020] 17

Fear Conditioning measures in PsPM – Pupil Size Responses



To investigate a placebo-controlled fear memory intervention with at least 80% power at α = .05 in a one-tailed test, under the assumption of equal variance in control and intervention groups (best-case scenario) with a fear memory reduction of at least 50%

Fear Conditioning measures in PsPM – Pupil Size Responses



	Cohen's d	Sample size
Peak scoring	0.60	278
PsPM	0.82	150

[Korn et al. 2017; Bach & Melinscak 2020] ¹⁹

Fear Conditioning measures in PsPM – Pupil Size Responses



Fear Conditioning measures in PsPM – Fear-Conditioned Bradycardia



Conditioned stimuli (CS) \rightarrow parasympathetic neural inputs \rightarrow HPR

Fear Conditioning measures in PsPM – Fear-Conditioned Bradycardia



Exp 1: 29 participants;

Visual CSs;

3.5 s SOA; 50% reinforcement

Exp 3: 19 participants;

Visual CSs; trace fear conditioning; 4 s SOA; 50% reinforcement

Exp 5: 18 participants;

Auditory CSs; 6 s SOA; 50% reinforcement

- Exp 2: 17 participants; Auditory CSs; 3.5 s SOA; 50% reinforcement
- Exp 4: 17 participants; Visual CSs; 3.5 s SOA; 50% reinforcement

Fear Conditioning measures in PsPM – Fear-Conditioned Bradycardia



- A gamma probability density function, together with its time derivative, in a General linear model (GLM)
- Condition-by-condition
- US-locked
- Experiments with different CS types and SOA

Fear Conditioning measures in PsPM – Fear-Conditioned Bradycardia

	Weighted average effect size (Cohen's d)
PsPM	0.97

Fear Conditioning measures in PsPM – Fear-Conditioned Bradycardia

	Cohen's d	Sample size
PsPM	0.97	108

Fear Conditioning measures in PsPM – Fear-Conditioned Bradycardia

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Fear Conditioning measures in PsPM – Respiration Amplitude Responses

Conditioned stimuli (CS) \rightarrow neural inputs \rightarrow RAR

Fear Conditioning measures in PsPM – Respiration Amplitude Responses

Exp 1: 33 participants; Visual CSs; 3.5 s SOA; 50% reinforcement Exp 2: 19 participants; Visual CSs; trace fear conditioning 4 s SOA; 50% reinforcement Exp 3: 20 participants; Visual CSs; 3.5 s SOA; 50% reinforcement Exp 4: 16 participants; Visual CSs; 3.5 s SOA; 50% reinforcement Exp 5: 18 participants; Auditory CSs; 6 s SOA; 50% reinforcement

Fear Conditioning measures in PsPM – Respiration Amplitude Responses

- A gamma probability density function, with ER + LR, in a General linear model (GLM)
- Condition-by-condition
- Possibly US-locked
- Model of ER + LR for experiments with short SOA

Fear Conditioning measures in PsPM – Respiration Amplitude Responses

Experiment	Model of ER + dt	Model of ER + LR
Exp 2	0.40	0.83
Exp 3	0.64	0.59
Exp 4	0.29	0.64
Exp 5	0.71	0.38
Exp 1 retention	0.20	0.42

	Weighted average effect size (Cohen's d)
PsPM	0.61

Fear Conditioning measures in PsPM – Respiration Amplitude Responses

	Cohen's d	Sample size
PsPM	0.61	268

[Castegnetti et al. 2017; Bach & Melinscak 2020] 31

Fear Conditioning measures in PsPM – Respiration Amplitude Responses

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Fear Conditioning measures in PsPM – Fear-Potentiated Startle

Conditioned stimuli (CS) + Startle probe → neural inputs → orbicularis oculi responses (SEBR)

Fear Conditioning measures in PsPM – Fear-Potentiated Startle

- A gamma probability density function, with flexible latency, in a General linear model (GLM)
- Trial-by-trial
- Startle-probe-elicited
- Experiments with startle sounds
- 3-5 trials for fear memory retention assessment

Fear Conditioning measures in PsPM – Fear-Potentiated Startle

			Experiment 2			Experiment 3			Experiment 4		
#	Model description	t(19)	р	Cohen's d	t(14)	р	Cohen's d	t(14)	р	Cohen's d	
M4ST	Best model-based method	5.21	<.0001	1.17	3.09	<.05	0.80	3.12	<.01	0.81	
B1	Barker et al. (2014)	4.51	<.001	1.01	3.10	<.05	0.80	3.23	<.01	0.96	
Br	Bradford et al. (2014)	5.21	<.0001	1.17	2.69	<.05	0.69	3.72	<.005	0.96	
G1	Grillon et al. (1991)	4.49	<.001	1.00	3.30	<.01	0.85	0.92	.37	0.24	
G2	Balderston et al. (2015)	4.80	<.001	1.07	3.00	<.05	0.77	4.63	<.001	1.20	

 Table 3. Paired T Test for the Difference Between CS+/CS- for Different Methods

Table 4. Paired T Test for the Difference Between CS+/CS- for Normalized Estimates from Different Methods

			Experiment 2			Experiment 3			Experiment 4		
#	Model description	t(19)	р	Cohen's d	t(14)	р	Cohen's d	t(14)	р	Cohen's d	
M4ST	Best model based method	5.08	<.0001	1.14	3.67	<.01	0.95	3.70	<.005	0.96	
B1	Barker et al. (2014)	4.88	<.001	1.09	3.84	<.01	0.99	4.12	<.005	1.06	
Br	Bradford et al. (2014)	5.23	<.0001	1.17	2.98	<.05	0.77	3.68	<.005	0.95	
G1	Grillon et al. (1991)	4.48	<.001	1.00	4.54	<.001	1.17	1.17	.26	0.30	
G2	Balderston et al. (2015)	4.61	<.001	1.03	3.75	<.01	0.97	4.24	<.001	1.10	

Exp 1: 19 participants;

no manipulation except acoustic startle probes

Exp 2: 20 participants;

Visual CSs; retention under extinction 7 days after acquisition

3.5 s SOA; 50% reinforcement

Exp 3: 30 participants;

Visual CSs; retention under extinction 1 day after acquisition

3.5 s SOA; 50% reinforcement

Exp 4: 14 participants;

Visual CSs; acquisition

3.5 s SOA; 50% reinforcement; startle probes in 25% of CS+US- and 25% of CS- trials

[Khemka et al. 2017; Bach & Melinscak 2020]

Fear Conditioning measures in PsPM – Fear-Potentiated Startle

			Experiment 2			Experiment 3			Experiment 4		
#	Model description	t(19)	р	Cohen's d	t(14)	р	Cohen's d	t(14)	р	Cohen's d	
M4ST	Best model-based method	5.21	<.0001	1.17	3.09	<.05	0.80	3.12	<.01	0.81	
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G2	Balderston et al. (2015)	4.61	<.001	1.03	3.75	<.01	0.97	4.24	<.001	1.10	

	Weighted average effect size (Cohen's d)
Peak Scoring G2 (non-normalized)	0.91
Peak Scoring G2 (normalized)	1.01
PsPM (normalized)	0.96
PsPM (non-normalized)	0.80

Fear Conditioning measures in PsPM – Fear-Potentiated Startle

	Cohen's d	Sample size
Peak Scoring G2 (non-normalized)	0.91	122
Peak Scoring G2 (normalized)	1.01	102
PsPM (normalized)	0.96	110
PsPM (non-normalized)	0.80	156

Fear Conditioning measures in PsPM – Fear-Potentiated Startle

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Find startle sound onsets Translate continuous sound channel to the given data fil option threshold, passed in the minimum amplitude of a This branch contains 5 items • Data File • Channel	d data into an event marker channel. The function adds a new marker te containing the sound data and returns the added channel number. The n percent to the maximum amplitude of the sound data, allows to specify sound to be accepted as an event. s:	Preprocess startle eyeblink Preprocess startle eyeblink three steps: Initially the da and 470 Hz. Then, Mains Finally, the data is smoot constant of ans (= cutoff a the input data must be a requirement for startle eyeb References:	EMG k EMG data for further analysis. Noise in EMG data will be removed in ta is filtered with a 4th order Butterworth filter with cutoff frequencies 50 Hz frequency will be removed using a notch filter at 50 Hz (can be changed). hed and rectified using a 4th order Butterworth low-pass filter with a time 153.05 Hz). The applied filter settings are according to the literature. While n 'erng' channel, the output will be an 'erng_pp' channel which is the link GLM.	Model Filename Specify file name for the res A string is entered. The character array may he	Specify sulting model. rve arbitrary size.	Dependency

Fear Conditioning measures in PsPM – Summary

Measure	Cohen's d	Sample size
SCR peak scoring	0.44	514
SCR model-based	0.75	174
HPR model-based	0.97	108
RAR model-based	0.65	236
PSR peak scoring	0.60	278
PSR model-based	0.82	150
Peak Scoring G2 (non-normalized)	0.91	122
Peak Scoring G2 (normalized)	1.01	102
SEBR model-based (normalized)	0.96	110
SEBR model-based (non-normalized)	0.80	156

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 - Pavlovian-to-Instrumental Transfer
 - Scanpath Length / Speed

Pavlovian-to-Instrumental Transfer (PIT)

	Pavlovian State					
Instrumental	Appetit	ive US	Aversive US			
Behaviors	Excitor (CS+)	Inhibitor (CS-)	Excitor (CS+)	Inhibitor (CS-)		
Approach	1	\downarrow	\downarrow	1		
Avoidance	\downarrow	\uparrow	1	\downarrow		

Pavlovian-to-Instrumental Transfer (PIT)

Pavlovian-to-Instrumental Transfer (PIT)

Pavlovian-to-Instrumental Transfer (PIT)

Model	Model Description	df	LBF	t	p	d
PIT #1	Response Rate in Withdraw Go trials *	34	reference	2.37	.024	.40
PIT #2	Response Rate in Withdraw Go trials in block 1	34	-0.62	2.51	.017	.42
PsPM #1	Heart Period	34	-11.67	4.61	< .001	.78
PsPM #2	Skin Conductance Responses	34	-8.05	3.98	< .001	.67
PsPM #3	Pupil Size	34	-3.17	3.06	.004	.52

Weak points:

- Effect size
- Complicated process

Scanpath Length (°, SPL)

- Attention
 - priority to fear-related cues
 - contribute to survival

- inconsistency of selective attention to CS+ compared to CS-

- fixation
- saccades

Experiment (Data set code)	CS	SOA	ITI	Fixation cross	Sample Size
Exploratory Exp 1 (PIT1)	visual	3.0	2.5 s	only in ITI	21
Confirmatory Exp 2 (PIT2)	visual	3.5	7-11 s	only in ITI	35
Generalisability Exp 3 (ViS)	visual	3.5	7-11 s	only in ITI	26 (25 for SCR)
Generalisability Exp 4 (PubFe)	auditory	3.5	7, 9, 11 s	always	22

Scanpath Length (°, SPL)

Exploratory Exp 1								
		3.0 s	2.5 s	2.0 s	1.5 s	1.0 s	0.5 s	GLM
df		20	20	20	20	20	20	20
LBF		0.00	0.18	-0.17	2.32	3.81	5.71	-0.48
g		0.63	0.62	0.63	0.51	0.43	0.30	0.65
			Conf	rmatory	Exp 2			
	3.5 s	3.0 s	2.5 s	2.0 s	1.5 s	1.0 s	0.5 s	GLM
df	34	34	34	34	34	34	34	34
LBF	0.00	-1.53	-4.85	-6.69	-4.86	-0.91	1.42	-5.27
g	0.47	0.52	0.62	0.68	0.62	0.50	0.41	0.63

* Each time window is defined as time period before US onset

Scanpath Length (°, SPL)

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CONTENTS

- Comparison of Models in PsPM
 - Skin Conductance Response
 - Pupil Size Response
 - Fear-Conditioned Bradycardia
 - Respiration Amplitude Responses
 - Fear-Potentiated Startle

- New Methods
 - Pavlovian-to-Instrumental Transfer
 - Scanpath Length / Speed

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THANK YOU!

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