Supplementary Material

_BDNF_val66met affects neural activation pattern during fear conditioning and 24h delayed fear recall

1. Analyses for all three genotype groups

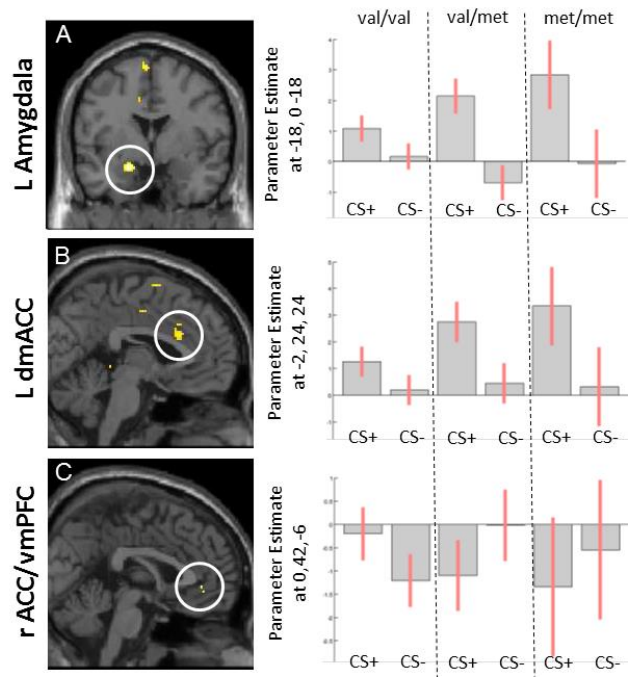
Additional second level models for the categorical regressors were set up that were identical to the second level models described in the main manuscript, except that the factor group consisted of three levels (val/val, val/met, met/met). Note that these analyses were exploratory due to the low number of homozygous met-individuals and mainly serve the purpose to further explore the main effects reported in the main manuscript.

1.1. Acquisition

Met-carrier > val/val

During fear acquisition, the additional analyses also showed an effect of BDNFval66met genotype on right amygdala activation for the contrast CS+>CS- in met-carriers>val/val (x,y,z= 18,0,18;Z=5.02, $p_{FWE(wholebrain)}$=0.011). Here carriers of one and two met-alleles were modelled separately in the second level model but for the statistical test treated as the same group. Extracted parameter estimates suggest an allele-load effect of *BDNF*val66met on right amygdala activation in this contrast (see **supplementary Figure 1A**).

Additional genotype-dependent differences suggesting an allele-load effect were observed in the same contrast in the left dorsomedial ACC (x,y,z= 2,24,24;k=33; Z=3.49, p<0.001 uc, see **supplementary Figure 1B**)) and the left inferior frontal cortex (x,y,z= -46,16,10; k=101; Z=4.09, p<0.001 uc), whereas effects in the left putamen (x,y,z= -18,12-8;k=46; Z=3.99, p<0.001 uc), as well as the supplementary motor area (x,y,z= -6,4-70;k=36; Z=4.53, p<0.001 uc), the mid ACC (x,y,z= -8,-12,44;k=39; Z=3.72, p<0.001 uc), the precentral gyrus (x,y,z= --20,-22,72;k=51; Z=4.32, p<0.001 uc) and a cluster in the parietal lobe (x,y,z= -36,-22,50;k=52; Z=3.69, p<0.001 uc) were mainly driven by high parameter estimates to the CS+ in met-homozygotes (data not shown).



Supplementary Figure 1. Activation in the contrast CS+> CS- (categorical) for met-carriers > val/val in the left amygdala (**A**) and the dmACC (**B**) and for val/val > met-carriers in the rostral ACC/vmPFC (**C**).

Images are thresholded at p<0.001(uc) for illustrative purposes. Error bars represent s.e.m. and beta estimates are derived from peak coordinates.

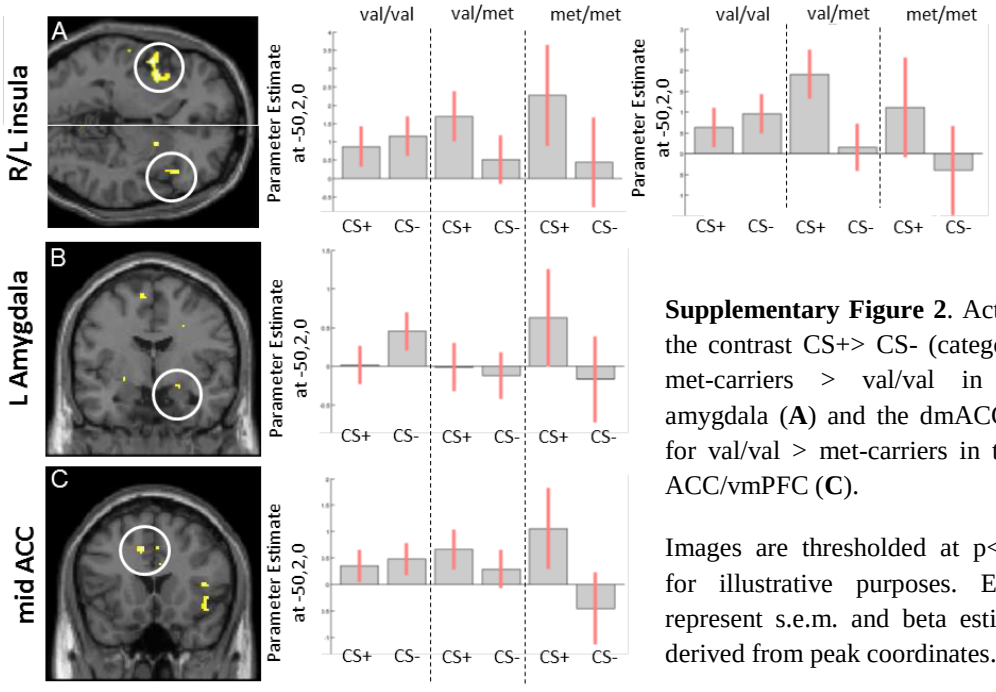
Val/val > met-carrier

No area showed significant higher activation in the contrast CS+>CS- for val-homozygotes vs. met/met at p=0.001uc. At a more lenient threshold of 0.01uc weak activation in the vmPFC area observed in the main analyses of the manuscript was observed (x,y,z= -0,42,-6;k=1; Z=2.36, p=0.009 uc). Here a dominant effect of the met-allele rather than an allele-dose effect was suggested by the parameter estimates (see **supplementary Figure 1C**).

1.2. Early Extinction

Met-carrier > val/val

During fear acquisition, the additional analyses with all three genotype groups also showed an effect of *BDNF*val66met genotype on the activation of the right (x,y,z= -50,2,0;k=65; Z=4.40, p<0.001 uc) and left (x,y,z= 44,22,-8;k=154; Z=3.70, p<0.001 uc) insula, the left amygdala (x,y,z= 22,-4,-12;k=3; Z=3.20, p=0.001 uc) and the left mid ACC (x,y,z= -10,18,38;k=98; Z=3.90, p<0.001 uc). No hippocampus activation differences were observed. Here carriers of one and two met-alleles were modelled separately in the second level model but for the statistical test treated as the same group. Extracted parameter estimates from these regions rather suggest an allele-load effect (with the exception of the left insula) of *BDNF*val66met on in this contrast (see **supplementary Figure 2A,B,C**).



Supplementary Figure 2. Activation in the contrast CS+> CS- (categorical) for met-carriers > val/val in the left amygdala (**A**) and the dmACC (**B**) and for val/val > met-carriers in the rostral ACC/vmPFC (**C**).

Images are thresholded at p<0.001(uc) for illustrative purposes. Error bars represent s.e.m. and beta estimates are derived from peak coordinates.

Val/val > met-carrier

No area showed significant higher activation in the contrast CS+>CS- for val-homozygotes vs. met/met at p=0.001uc.

2. Exploratory whole brain analyses

Supplementary Table 1. Peak grey matter coordinates based on the WFU Pickatlas (based on the analyses reported in the main document) with a spatial extend of k≥10 at an exploratory threshold of p<0.001 uncorrected. * indicates FWE-corrected p-values (whole brain)

Phase	Contrast	cat/pm	comparison	region	x,y,z	Z	k	p
Conditioning	CSP>CSM	cat.	met-carrier > val/val	L amygdala	-18,0,-18	4.04	10	<0.001
				precentral lobule	0,-18,68	3.81	17	<0.001
				R precentral	38,-16,62	3.77	10	<0.001
		cat.	val/val > met-carrier	R ACC/vmPFC	22,44,-8	3.84	16	<0.001
		pm.	met-carrier > val/val	none				
		pm.	val/val > met-carrier	L supp. Motor area	-4,-18,54	3.84	37	<0.001
				L temporal pole	36,6,-28	3.74	14	<0.001
				R Sup. temporal	58,-10,-4	3.68	35	<0.001
				R ACC	8,44,4	3.68	24	<0.001
				cerebellum	26,-46,-40	3.65	17	<0.001
				L inf. frontal	-36,30,10	3.58	22	<0.001
				L inf. frontal	-38,22,16	3.25	14	0.001
Extinction (1st half)	CSP>CSM	cat.	met-carrier > val/val	L thalamus	-6,-8,-4	5.33	58	0.005*
				L insula	-50,2,0	4.80	80	0.059*
				L putamen	-24,-6,-8	4.77	39	0.068*
				cerebellum	2,-60,-30	4.48	55	<0.001
				R lateral PFC	36,60,12	4.40	25	<0.001
				R postcentral gy	66,-16,16	4.28	62	<0.001
				R rodlandic operc.	54,-26,20	4.20	41	<0.001
				R post. Insula	44,-16,20	4.05	24	<0.001
				R sup. temporal	66,-16,4	4.02	20	<0.001
				R supramarg. gy.	66,-40,30	3.99	14	<0.001
				R ant. Insula	40,28,-4	3.97	53	<0.001
				cerebellum	-34,-54,-28	3.89	17	0.001
				R. sup. temporal	52,-26,10	3.78	20	0.001
				R insula	50,4,-4	3.76	22	0.001
				R insula	34,4,8	3.70	31	0.001
				L insula	-36,6,-2	3.66	11	0.001
				mid ACC	2,14,40	3.40	12	0.001
		cat.	val/val > met-carrier	L precuneus	-18,-46,14	4.30	45	<0.001
				mid Cingulum	18,4,40	4.26	23	<0.001
		pm	met-carrier > val/val	none				
		pm.	val/val > met-carrier	L somatosensory	-24,-50,56	3.70	10	<0.001
				L insula	-34,14,-10	3.66	25	<0.001
Extinction (2nd half)	CSP>CSM	cat.	met-carrier > val/val	none				
		cat.	val/val > met-carrier	L lateral PFC	-44,50,10	4.14	49	<0.001
				R lateral PFC	42,54,6	3.91	18	<0.001
				L mid frontal	-32,30,34	3.67	17	<0.001
				R mid frontal	34,46,32	3.40	13	<0.001