Autism Spectrum Disorder is a Risk Factor for PTSD-like Memory Formation

A.S. Al Abed^{1*}, A. Sellami^{2,3}, A. Marighetto^{2,3}, A. Desmedt^{2,3}, N. Dehorter¹

Affiliations

¹ Eccles Institute of Neuroscience, John Curtin School of Medical Research, The Australian National University, Canberra, ACT, Australia

² Neurocentre Magendie, Physiopathologie de la plasticité neuronale, U1215, INSERM, F-33000 Bordeaux, France

³ Université de Bordeaux, F-33000 Bordeaux, France.

* Correspondence to: shaam.alabed@anu.edu.au

ABSTRACT

The predisposition of Autism Spectrum Disorder (ASD) to Post-Traumatic Stress Disorder (PTSD) remained to be established. Here, we show that exposure to a single mild stressful event induces maladaptive memory, which recapitulates all features of PTSD, and is associated with the broad dysfunction of the prefrontal-hippocampo-amygdalar network. Using optogenetics, we demonstrate that prefrontal cortex hyperactivation triggers this PTSD-like memory. Finally, we show that recontextualization of the traumatic event normalizes maladaptive memory in ASD conditions. Overall, this study provides the first direct demonstration that ASD represents a risk factor for PTSD and uncovers new mechanisms that underlie pathological memory formation.

Main text:

Beyond core deficits in social interactions and repetitive movements(1,2), autism spectrum disorder (ASD) presents with cognitive defects, including hyper-reactivity to sensory stimuli(3) and altered declarative memory(4). Such a combination of impairments suggests a potential predisposition for developing post-traumatic stress disorder (PTSD), in which an extreme stress induces an altered memory of an event(1,5). In line with recent studies in humans positing a co-occurrence of these two pathologies(6–8), ASD and PTSD display common behavioral features including impaired emotional regulation, cognitive rigidity, and fragmented autobiographical memory(4). Yet, the overlap between the two disorders remains poorly explored.

To determine whether ASD is a risk factor for PTSD, we used the Contactin-associated protein 2 knock out (*Cntnap2* KO) mouse model, which replicates the core behavioral symptoms of ASD(2,9,10). We first assessed the ability of wild-type (WT) and *Cntnap2* KO mice to form adaptive fear memory in a contextual fear conditioning paradigm, modified from a model of PTSD-like memory(11,12). This paradigm combines a tone *unpaired* to a mild electric foot-shock, thus making the conditioning context the only relevant predictor of the threat (**Figure 1A**). 24 hours' post conditioning, WT mice displayed an adaptive contextual fear memory, characterized by a marginal freezing response when exposed to the tone in a neutral context (i.e. tone test; **Figure 1B left panel**) and a strong fear response to the conditioning context (i.e. context test; **Figure 1B right panel**). *Cntnap2* KO mice demonstrated a similar memory pattern to WT mice, indicating normal adaptive fear memory. To assess the impact of stress on their learning ability, we submitted the mice to a 30min-restraint stress, 24h before conditioning (**Figure 1A**). Under these conditions, WT mice again demonstrated normal contextual fear memory (**Figure 1C**). In contrast, the *Cntnap2* KO mice showed a strong and specific fear response to the tone combined to low freezing to the conditioning context (**Figure 1C**). Strikingly, this maladaptive memory profile mimics PTSD-related memory, by combining intrusive *sensory hypermnesia* for an irrelevant, yet salient element of the trauma, with a partial *amnesia* of the surrounding context(1,5,13). As a major feature of PTSD-like memory is that it persists in the long term(1) (**Figure 1C**), we re-tested the *stressed* autistic mice 21 days after conditioning. Remarkably, the *Cntnap2* KO group exhibited an abnormally high fear response to the tone, and low freezing to the conditioning context, whilst WT mice display normal fear memory (**Figure 1D**). Our results hence demonstrate that the *Cntnap2* KO mice display an abnormal (cue-based) fear memory that lasts across time and is resistant to extinction (i.e. repeated presentation of the tone and conditioning context). Since we found no difference in the reactivity

to the electric foot-shock or the tone presentation between WT and *Cntnap2* KO mice (**Figure S1A**), we concluded that the altered memory did not stem from different sensory processing(3). Additionally, the *Cntnap2* KO mice showed significantly higher freezing levels when presented to a *similar* tone (3kHz) to the conditioning tone (1kHz), than compared to a white noise exposure (i.e. highly *dissimilar* from the conditioning tone; **Figure S1B**). These results indicate partial generalization of fear(11) when exposed to similar salient element of the traumatic event(1). We therefore demonstrate the increased susceptibility of the *Cntnap2* KO mice to develop a maladaptive memory that recapitulates all the characteristics of PTSD. To confirm that this profile is a feature of the autistic condition and not due to specific features of the *Cntnap2* KO mouse model, we submitted the phosphatase and tensin homolog conditional knockout (*Pten* cKO) mouse model of autism(14) to the restraint stress and unpaired fear conditioning paradigm. The *Pten* cKO mice also displayed maladaptive memory (**Figure 1E**), overall proving that the autistic condition is a risk factor for developing PTSD-like memory.

Maladaptive memory is underpinned by imbalanced neuronal activity within the prefrontal-hippocampo-amygdalar network, in both mice and humans(15,16). Interestingly, the medial prefrontal cortex (mPFC), hippocampus, and amygdala have also been implicated in the pathophysiology of ASD(17–19). To uncover potential divergent mechanisms in PTSD and ASD, we mapped the brain activations induced by re-exposure to the conditioning context (**Figure 2A**). We found a widespread imbalance in recall-induced c-Fos expression in the stressed *Cntnap2* KO mice compared to the stressed WT mice (**Figure 2B**). In addition, analyses of pair-wise between-structure correlations of c-fos expression (**Figure 2C**) demonstrated a drastic alteration in the functional connectivity of the autistic mice. In particular, we observed a hypoactivation of the hippocampus and amygdala, as well as a hyperactivation of the mPFC. These different levels of activation are consistent with those previously reported in ASD (17,18,20) but are opposite to the patterns observed in PTSD (i.e. mPFC hypoactivation and amygdala hyperactivation(11)). Such a discrepancy between the behavioral impairments and the expected alterations in brain activations has been previously observed in autism. For instance, while increased amygdala activity underlies excessive anxiety(21), it has been shown that ASD patients display anxiety traits in spite of amygdala hypofunction(17). With this in mind, our results suggest that rather than the activation levels of a particular structure (i.e hypo- or hyper-activation), the alterations of the default state network in ASD could be responsible for the behavioral defects.

Within the prefrontal-hippocampo-amygdalar network, the mPFC underpins a key function in the pathophysiology of both PTSD and ASD (16,18,22). In addition, modulating the activity of the mPFC normalizes the core symptoms of ASD(20). We investigated the causal role of the mPFC in the overlap between ASD and PTSD. Using optogenetic manipulation during the conditioning session, we determined the consequences of counteracting mPFC hyper-activation on memorization (**Figure 2D**). We found that, unlike the control GFP-infected group, the ArChT-expressing stressed *Cntnap2* KO mice displayed normal memory of the stressful event (i.e. no fear responses to the irrelevant tone, and high fear responses to the predictive context; **Figure 2E**). We concluded that mPFC inhibition in stressed ASD mice prevents PTSD-like memory formation. To then assess whether combining the acute mild stress with mPFC hyperactivation could elicit the development of pathological memory, we employed optogenetic stimulation during conditioning in stressed WT mice. Unlike GFP-injected mice, ChR2-expressing WT mice displayed a strong fear response to the tone, combined with a decreased response to the context (**Figure 2F**). Together, these results demonstrate for the first time that mPFC hyperactivation during a trauma, following an acute mild stress, leads to PTSD in both autistic and WT mice. However, previous studies reported mPFC hypoactivation in patients suffering from PTSD(16). We propose that activation levels could differ according to the stage of memorization. Indeed, while hypoactivation of the mPFC could be associated with the recall of a traumatic event, our study manipulates the activity of the mPFC during the encoding of the trauma. Future studies should investigate whether mPFC hyperactivity during memory formation could result in circuit changes, ultimately leading to mPFC hypofunction during long-term memory recall. In addition, the maintenance of the excitation/inhibition balance in the mPFC, controlled by parvalbumin interneurons(23), is critical for adapted fear memorization(22) and altered in ASD (20). Deciphering the molecular mechanisms underlying the fine-tuning of cortical interneuron activity(24) will provide critical insights into the pathophysiology of both ASD and PTSD.

Despite the divergence observed in the activation levels of the amygdala and the mPFC, we uncovered a common pattern of activation, shared between the ASD and PTSD conditions: a hypoactivation of the hippocampus (**Figure 2B**). The key function of the hippocampus in the generation of PTSD has been recently demonstrated and the lack of hippocampal activation has been shown to prevent the encoding of the context surrounding a stressful event, hence shifting the fear towards a salient, irrelevant cue associated with the trauma(12,13). Our results confirm the pivotal role of the hippocampus-dependent contextualization capacity in determining the nature of the memory formed (*i.e.* normal vs. pathological memory) during a stressful event, in both ASD and PTSD.

We next examined the malleability of the pathological memory developed in ASD conditions. We used recontextualization(12), a behavior-based rehabilitation strategy, which has been suggested as a therapeutic strategy in PTSD patients(13). The protocol consists of re-exposing the *Cntnap2* KO mice displaying long-term PTSD-like memory to the original tone in the conditioning context with no footshock (**Figure 3A**). During the recontextualization session, the stressed *Cntnap2* KO mice replicated the amnesia to the conditioning context, followed by a strong and high fear response to the tone (**Figure 3B**). 24h later, they exhibited normal, contextualized fear memory (**Figure 3C**). Together, these results demonstrate that pathological memory can be reshaped into adapted fear memory. By reactivating the traumatic memory in the original environment, recontextualization allows the re-allocation of trauma representation into specific context, thereby suppressing abnormal hypermnnesia(12). While this is promising, one caveat for the implementation of this procedure in patients will arise from being able to identify the origin of the trauma. Our results show that, contrary to a control population, in which PTSD-related memory is triggered by an extreme stress(1), a single mild stress is sufficient to produce pathological memory of an event in ASD. In line with the well-demonstrated impairments in coping with stress(3), we suggest that everyday life situations could ultimately become traumatizing in ASD. Yet, the current prevalence of PTSD in autism does not differ from the normal population(7). This low prevalence is most likely underestimated and could stem from the challenges of detecting PTSD in ASD(8). Finally, this work encourages awareness of the potential consequences of stress in other psychiatric disorders, in which declarative memory formation is similarly impaired(25).

Overall, our study provides a new tool to further dissect the overlap between PTSD and ASD and the underlying alterations in emotional memory. It encourages future research to enhance detection and implementation of therapeutic strategies to pave the way towards alleviating the uncontrollable reactivation of traumatic memory in autism. This is particularly timely in the context of environmental pressure such as the COVID-19 pandemic(26), in which lockdowns and curfews disrupt routines and may produce long-lasting cognitive impairments in vulnerable populations.

Methods and Material

Mice. 3 to 5-month-old naive mice were individually housed in standard Makrolon cages, in a temperature- and humidity-controlled room under a 12-h light/dark cycle (lights on at 07:00), with *ad libitum* access to food and water. We used both males and females to minimize the number of mice produced in this study. WT and KO mice (*Cntnap2* KO, Jackson ID: #017482(10)) were non-littermates, derived from breeders of the same colony. *Pten* control (*Pten*^{F/F}) and cKO mice (*Pten*^{F/F}; *Emx-Cre*) were male littermates, kindly provided by Dr Andreas Frick (Neurocentre Magendie, Bordeaux University, France). All experiments took place during the light phase. Every effort was made to minimize the number of animals used and their suffering. All procedures were conducted in accordance with the European Directive for the care and use of laboratory animals (2010-63-EU) and the animals care guidelines issued by the animal experimental committee of Bordeaux University (CCEA50, agreement number A33-063-099; authorization N°21248), and from the Australian National University Animal Experimentation Ethics Committee (protocol numbers A2018/66 and A2020/26).

Fear conditioning procedure. To assess the quality of the fear memory in the *Cntnap2* WT and KO mice, we used the only model available that allows the assessment of both memory components of PTSD (emotional hypermnnesia and contextual amnesia) in mice(11). Habituation (Day 0): The day before fear conditioning, mice were individually placed for 4 min into a white squared chamber (30x15cm, Imetric),

France) with an opaque PVC floor, in a brightness of 40 lux. The box was cleaned with 1% acetic acid before each trial. This pre-exposure allowed the mice to acclimate and become familiar with the chamber later used for the tone re-exposure test. **Acute mild stress:** To elicit stress response, we performed a 30min restraint stress under bright light (100Lux). Stressed mice were taken to a neutral room and placed into a perforated 50mL Falcon® tube allowing air circulation. Non-stressed control mice were taken to the same room for 30min but were kept in their home cage. **Conditioning (Day 1):** Acquisition of fear conditioning was performed in a different context, a transparent squared conditioning chamber (30x15 cm) in a brightness of 100 lux, given access to the different visual-spatial cues of the experimental room. The floor of the chamber consisted of 30 stainless-steel rods (5 mm diameter), spaced 5 mm apart and connected to the shock generator. The box was cleaned with 70% ethanol before each trial. All animals were trained with a tone-shock un-pairing procedure, meaning that the tone was non-predictive of the footshock occurrence. This training procedure, fully described in previous studies(11), promotes the processing of contextual cues in the foreground. Briefly, each animal was placed in the conditioning chamber for 4 min during which it received two tone cues (65 dB, 1 kHz, 15 s) and two foot-shocks (squared signal: 0.4 mA, 50 Hz, 1 s), following a pseudo-randomly distribution. Specifically, animals are placed in the conditioning chamber and receive a shock 100 s later, followed by a tone after a 30s interval. After a 20s delay, the same tone and shock spaced by a 30s interval were presented. Finally, after 20s, mice were returned to their home cage. As the tone was not paired to the footshock, mice selected the conditioning context (i.e. set of static background contextual cues and odor that constitutes the environment in which the conditioning takes place) and not the tone as the correct predictor of the shock (**Figure 1A**, Day1). **Memory Tests (Day 2):** 24 hours after conditioning, mice were submitted to two memory retention tests and continuously recorded for off-line second-by-second scoring of freezing by an observer blind to experimental groups. Mouse freezing behavior, defined as a lack of movement (except for respiratory-related movements), was used as an index of conditioned fear response(27). Mice were first submitted to the tone re-exposure test in the safe, familiar chamber during which three successive recording sessions of the behavioral responses were previously performed: one before (first 2 min), one during (next 2 min), and one after (2 last min) tone presentation (**Figure 1A**, Day 2). Conditioned response to the tone was expressed by the percentage of freezing during tone presentation, compared to the levels of freezing expressed before and after tone presentation (repeated measures on 3 blocks of freezing). The strength and specificity of this conditioned fear was attested by a tone ratio that considers the percentage of freezing increase to the tone with respect to a baseline freezing level (i.e., pre- and post-tone periods mean). The tone ratio was calculated as follows: $[\% \text{ freezing during tone presentation} - (\% \text{ pre-tone period freezing} + \% \text{ post-tone period freezing})/2] / [\% \text{ freezing during tone presentation} + (\% \text{ pre-tone period freezing} + \% \text{ post-tone period freezing})/2]$. Two hours later, mice were submitted to the context re-exposure test. They were placed for 6 min in the conditioning chamber. Freezing to the context was calculated as the percentage of the total time spent freezing during the successive three blocks of 2-min periods of the test.

Assessment of the persistence of PTSD-like fear memory. To demonstrate that the PTSD-like memory was long-lasting, mice were again submitted to the two memory tests (tone-test and context-test spaced out of 2h, as in day 2), 20 days after fear conditioning.

Optogenetic manipulation of the mPFC. Surgery: Mice were injected bilaterally 4 weeks before behavioral experiments with an Adeno-Associated Virus (AAV) to inhibit (AAV5-CaMKII α -ArchT-GFP, UNC Vector Core) or activate glutamatergic neurons (AAV5-CaMKII α -ChR2 (H134R)-EYFP, UNC Vector Core). Control mice were injected with an AAV expressing GFP only (AAV5-CaMKII α -GFP). We used glass pipettes (tip diameter 25-35 μ m) connected to a picospritzer (Parker Hannifin Corporation) into the mPFC (0.1 μ L/site; AP +1.9mm; L $\pm$ 0.35mm; DV -1.3mm). Mice were then implanted with bilateral optic fiber implants, 10 days before behavior (diameter: 200 μ m; numerical aperture: 0.39; flat tip; Thorlabs) directed to the mPFC (AP: +1.8, L: $\pm$ 1.0, DV: -1.3, θ : 10°). Implants were fixed to the skull with Super-Bond dental cement (Sun Medical, Shiga, Japan). Mice were perfused after experiments to confirm correct placements of fibers (**Figure S2**). For optogenetic manipulations, we used a LED (Plexon®) at 465nm with a large spectrum to allow the activation of both ArchT and ChR2. Light was continuously delivered to inactivate the mPFC, and was delivered at 5Hz (5ms ON, 195ms OFF) for mPFC activation. Mice were submitted to the fear conditioning

procedure described above and pyramidal cells of the mPFC were either inhibited or activated during the whole conditioning session. Mice were then immediately placed in the conditioning chamber and submitted to the fear conditioning paradigm. The next day, fear memory was tested as described above.

Recontextualization was performed as previously described(12). Briefly, two days after long-term testing (Day 23), mice were re-exposed to the tone cue in the conditioning context, without electric shock (**Figure 3**, Day 23). The first 2 min (pre-tone) allowed us to assess the level of conditioned fear to the conditioning context alone, while the conditioned response to the tone was assessed during the next 2 min, both by the percentage of freezing during the tone presentation and by the tone ratio described above. 24h later, fear expression was assessed by re-exposing the mice to the regular (i.e. separated from each other) tone and context tests (same tests as in day 2).

c-Fos immunohistochemistry. 90 minutes after the context test on Day 2, animals were perfused transcardially with 0.01M phosphate buffered saline (PBS) to eliminate blood and extraneous material, followed by 4% paraformaldehyde (PFA). Brains were postfixed for 36 hours in PFA. Tissues were sectioned at 40µm using a Leica 1000S vibratome and kept in a cryoprotective ethylene glycol solution at -20°C until processed for immunofluorescence. Sections were first washed and permeabilized, then non-specific binding sites were blocked by immersing the tissue in 10% normal donkey serum, 2% BSA in PBS-Triton during 2h. Tissues were then stained using the primary antibodies overnight: mouse anti-c-Fos (1:1000; Santa Cruz). After 3x 15' washes, we added anti-rabbit, anti-chicken, anti-mouse, Alexa 488 or 555 (1:200; Life Technologies) secondary antibodies for 2h. After 3x 15' washes slices were stain during 10' with DAPI (5µM; Sigma), mounted on Livingstone slides then covered with Mowiol (Sigma) and coverslip (Thermofisher). c-Fos staining was imaged using a Zeiss Axio Observer fluorescent microscope (20x objective). Stained sections of control and mutant mice were imaged during the same imaging. Immunofluorescence signals were quantified using the ImageJ (FIJI) software with routine particle analysis procedures, to obtain nuclear masks, divided by the area to obtain cell density per mm².

Statistics. Data are presented as the mean ± SEM error bar. Statistical analyses were performed using 2-sided ANOVA, followed by Fisher's PLSD *post-hoc* test when appropriate. Analyses were performed using the StatView software. Normality of the data was confirmed using the Kolmogorov–Smirnov test. Statistical significance was considered at P<0.05.

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Acknowledgements: We would like to thank Dr Andreas Frick for the *Pten* cKO mice. We thank all the personnel of The Australian Phenomics Facility and of The Neurocentre Magendie involved in mouse care.

Funding: This work was supported by The Australian National University (Futures Scheme Grant), the Institut National de la Santé et de la Recherche Médicale (INSERM), a Bordeaux Neurocampus grant by le Conseil Régional d'Aquitaine, and Centre National de la Recherche Scientifique (CNRS for AM's salary).

Authors Contributions: A.S.A., A.D., and N.D. designed Research. A.S.A. and A.S. performed the experiments. A.S.A analyzed the data. A.S.A., A.D., A.M., and N.D. discussed the results. A.S.A. and N.D. wrote the paper.

Competing interest: The authors declare no competing interests.

Data and material availability: All data is available in the main text or the supplementary materials.

Figures and Legends

Figure 1. *Cntnap2* KO mice display traumatic memory profile after mild stress. (A) Day 0: 30min restraint stress under a bright light. Day 1: contextual fear conditioning (2 unpaired tone-footshock presentations). Day 2: memory tests (right). Tone test: mice were played the tone alone, in a neutral context (grey box). Context test: reexposure to the conditioning context alone. (B) Non-stressed groups (WT: n=12; *Cntnap2* KO: n=13) displayed normal memory: an absence of fear response to the tone combined with a strong freezing to the context. (C) Stressed *Cntnap2* KO mice (n=14) displayed a specific fear response to the tone, compared to before (Pre) or after (Post) the tone (*repeated measures x genotype*: $F_{2,58}=8.660$; $p=0.0005$). Inset: ratio of the specific fear response to the tone in *Cntnap2* KO is significantly higher than that of WT (*genotype*: $F_{1,29}=5.643$; $p=0.0243$). WT mice (n=17) showed strong freezing to the context, significantly higher than *Cntnap2* KO mice (*genotype*: $F_{1,29}=19.158$; $p<0.0001$). (D) 21 days after conditioning, *Cntnap2* KO mice (n=6) still displayed maladaptive memory (Tone test: *Repeated measures x Genotype*: $F_{2,26}=15.098$; $p<0.0001$; Context test: *Genotype*: $F_{1,13}=8.937$; $p=0.0104$). WT mice (n=9) demonstrated normal memory. (E) Stressed *Pten* cKO mice displayed PTSD-like memory profile (n=8; tone test: *repeated measures x genotype*: $F_{2,26}=15.952$; $p<0.0001$; context test: *genotype*: $F_{1,13}=5.455$; $p=0.0362$). Data are presented as mean $\pm$ SEM. ***: $p<0.001$; **: $p<0.01$; *: $p<0.05$; Bracket shows interaction significance between freezing and genotype.

Figure 2. Description and manipulation of brain activity associated with fear memory. (A) Experimental paradigm for c-Fos quantification. **(B)** Context recall-induced brain activation in the dentate gyrus (DG; *Genotype*: $F_{1,12}=6.404$; $p=0.0264$), medial pre-frontal cortex (mPFC) ($F_{1,12}=5.469$; $p=0.0375$), and amygdala (lateral amygdala, LA; $F_{1,11}=25.094$; $p=0.0004$; basolateral amygdala, BLA; $F_{1,10}=0.721$; $p=0.4156$; central amygdala, CeA; $F_{1,10}=13.118$; $p=0.0047$). **(C)** Schematic representation of the two-by-two between-structure correlation matrices between c-fos density. Thickness of the lines represent the strength pair-wise positive (purple) or negative (turquoise) correlations. Data are presented as mean $\pm$ SEM. ***: $p<0.001$; **: $p<0.01$; *: $p<0.05$. **(D)** ChR2- or ArChT-AAV were delivered into the mPFC. Day1: optogenetic manipulation during the entire contextual fear conditioning session. Day2: memory tests **(E)** ArChT-KO mice (light blue; $n=3$; GFP: red; $n=11$) displayed a normal memory profile (Tone test: *repeated measures x condition*: $F_{2,28}=6.287$; $p=0.0064$; Context test: *condition*: $F_{1,14}=5.812$; $p=0.0329$). **(F)** mPFC stimulation in ChR2-expressing WT mice ($n=7$; dark blue) induced a PTSD-like memory (Tone test: *repeated measures x condition*: $F_{2,28}=17.397$; $p<0.0001$; Context test: *Condition*: $F_{1,14}=4.766$; $p=0.0465$), unlike GFP-infected WT mice ($n=9$; black). Data are presented as mean $\pm$ SEM. ***: $p<0.001$; **: $p<0.01$; *: $p<0.05$; Bracket shows interaction significance between freezing and genotype.

Figure 3. PTSD-like memory in the *Cntnap2* KO mice is reversed by trauma recontextualization. (A) Recontextualisation (ReContext.): conditioning tone re-played in the conditioning context, no footshock. Day 24: Memory tests. **(B)** WT mice displayed significantly higher freezing than *Cntnap2* KO mice ($n=9$ and 6 , respectively; *genotype*: $F_{1,13}=3.720$; $p<0.0001$). Tone presentation elicited a strong fear response in the *Cntnap2* KO only (*repeated measures x genotype*: $F_{2,26}=26.616$; $p<0.0001$). **(C)** Day 24: *Cntnap2* KO mice displayed a normal memory profile (tone test: *repeated measures x genotype*: ns; context test: *genotype*: ns). *Cntnap2* KO Pre Recontext. (light pink square): illustration of Day 2 fear response for comparison (as in Figure 1C). Data are presented as mean $\pm$ SEM. ***: $p<0.001$; **: $p<0.01$; *: $p<0.05$; Bracket shows interaction significance between freezing and genotype.