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Human serotonin transporter availability predicts fear conditioning

Fredrik Åhs [a,b,*], Andreas Frick [a], Tomas Furmark [a], Mats Fredrikson [a,b]

[a] Department of Psychology, Uppsala University, Uppsala, Sweden
[b] Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

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ABSTRACT

Serotonin facilitates fear learning in animals. We therefore predicted that individual differences in the capacity to regulate serotonergic transmission in the human neural fear circuit would be inversely related to fear conditioning. The capacity to regulate serotonergic transmission was indexed by serotonin transporter availability measured with [^{11}C]-DASB positron emission tomography. Results indicate that lower serotonin transporter availability in the amygdala, insula and dorsal anterior cingulate cortex predicts enhanced conditioned autonomic fear responses. Our finding supports serotonergic modulation of fear conditioning in humans and may aid in understanding susceptibility for developing anxiety conditions such as post-traumatic stress disorder.

1. Introduction

While central serotonin modulates negative affect (Ressler and Nemeroff, 2000), its etiological role in anxiety disorders is not fully understood. To understand the neural mechanisms of anxiety, animal studies often use fear conditioning paradigms, whereby a neutral cue subsequently elicits fear after associative aversive learning. In both animals (Maren and Quirk, 2004) and humans (Sehlmeyer et al., 2009; Mechias et al., 2010), the neural circuit underlying fear conditioning includes the amygdala, the anterior cingulate cortex (ACC) and the insula. The fear circuit of the brain, particularly the amygdala, is rich in serotonergic neurons (Barnes and Sharp, 1999) and several lines of evidence link serotonergic functions to fear conditioning. For example, blocking the serotonin transporter by administering acute doses of selective serotonin reuptake inhibitors (SSRIs) enhances fear conditioning by increasing extracellular serotonin in rodents (Burghardt et al., 2007), and reducing serotonin availability by acute tryptophan depletion compromises fear conditioning in humans (Attar et al., 2012). Molecular genetic studies demonstrate that markers of increased synaptic serotonin like, the short allele variant of the serotonin transporter gene-linked polymorphic region (5-HTTLPR), predict superior fear conditioning when compared to the long allele (Garpenstrand et al., 2001; Lonsdorf et al., 2009). The short allele of 5-HTTLPR has been coupled to conditioned fear responses in the insula (Hermann et al., 2012) and the amygdala (Klucken et al., 2013) paralleling findings in serotonin transporter knockout mice (Pang et al., 2011). In addition, high serotonin concentrations in the amygdala are associated with increased neural reactivity to emotional pictures in multimodal neuroimaging studies of serotonin transporter availability (Rhodes et al., 2007) and serotonin-1A receptor density (Fisher et al., 2006). Thus, serotonin may facilitate fear conditioning by modulating neural processing in the fear circuitry.

While previous studies support serotonergic modulation of conditioning, direct evidence relating serotonin in the human brain to fear conditioning is lacking. We therefore evaluated if fear conditioning is related to serotonin transporter availability, measured with [^{11}C]3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile ([^{11}C]-DASB) positron emission tomography (PET). Increased [^{11}C]-DASB uptake is associated with reduced synaptic serotonin (Lundquist et al., 2005), and low systemic serotonin levels attenuate conditioning (Attar et al., 2012). These findings formed the basis for our prediction of a negative correlation between conditioned skin conductance responses and [^{11}C]-DASB binding potential (BP) in the fear circuitry including the amygdala, insula and the anterior cingulate cortex (Sehlmeyer et al., 2009; Mechias et al., 2010).

To test this prediction, we combined serotonin transporter PET imaging with human fear conditioning data. During fear conditioning, a fear cue, CS+, consistently predicted the delivery of an aversive electric shock, while a control cue, CS−, was never paired with shock. Our primary measure of fear learning was the difference in autonomic responses between the CS+ and CS−.

* Corresponding author at: Department of Psychology, Uppsala University, Box 1225, 751 42 Uppsala, Sweden. Tel.: +46 18 471 5758; fax: +46 18 471 2400.
E-mail address: fredrik.ahs@psyk.uu.se (F. Åhs).

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2. Methods

2.1. Participants

Eight men and 8 women with a mean (±SD) age of 35 (±9.4) years were recruited to participate in the study. Exclusion criteria included psychiatric disorder, organic brain disorder, somatic disease, left-handedness, substance abuse, and pregnancy. The Structured Clinical Interview for DSM-IV (SCID; First et al., 1996) was administered to assess psychiatric symptoms. All participants refrained from tobacco, alcohol, and caffeine for 12 h, and from food for 3 h, before the PET investigations. None had participated in a PET study previously. The local ethical and radiation safety committees approved the study, and written informed consent was obtained from the participants.

2.2. Fear conditioning

All sixteen subjects underwent fear conditioning where two pictorial stimuli, a circle and a triangle counterbalanced for reinforcement, were displayed for 10 s. Prior to conditioning each stimulus was displayed 3 times to reduce orienting responses. During fear conditioning, the conditioned stimulus (CS+) always co-terminated with a 0.5 s electric shock delivered to the right forearm through two Ag–AgCl cup electrodes. The control stimulus (CS−) was never paired with shock. Each CS-type was displayed 6 times in a pseudo-randomized order with no more than two consecutive trials of each category. Because conditioned responses are not acquired during the first stimulus pairings, only the last 4 trials were used when computing skin conductance responses. No explicit information regarding contingencies was given. The intertrial interval varied between 15 and 35 s with a mean of 26 s. The intensity of the shock was determined by a work up procedure and terminated when subjects reported that the shock was uncomfortable but not painful. If subjects reported pain the shock level was adjusted accordingly. Fear conditioning was completed within 16–20 weeks after PET.

Skin conductance was recorded through two Ag–AgCl electrodes filled with isotonic electrolytic gel using Psylab (Contact Precision Instruments Inc., London, UK) using 100 Hz sampling rate. The signal was high pass filtered at 0.1 Hz. First interval responses show good temporal test–re-test stability (Fredrikson et al., 1993) ($r_{xy} = 0.72$) and skin conductance responses were quantified in a standard manner by subtracting the maximum value 1–4.5 s after CS onset from the mean skin conductance level in the 0.5 s time window immediately preceding CS onset (Dawson et al., 2000). SCRs less than 0 were treated as zero-responses. SCR was log-transformed (log(SCR + 1)) to reduce the influence of extreme values and deviation from normality. Because one participant had a value deviating > 5 SD she was excluded and the equipment failed for one additional participant, leaving 14 evaluated and entered into the statistical analyses.

The difference in SCR between CS+ and CS− was used as fear conditioning index because the CS− controls for reactivity differences unrelated to fear learning and the difference specifically reflects the fear memory (Agren et al., 2012).

2.3. Positron emission tomography

Participants were injected with an average of 405 (±23) MBq of [^{11}C]-3-amino-4-(2-dimethylaminomethylphenylsulfanyl)-benzonitrile ([^{11}C]DASB). Scanning was performed using a 32-ring ECAT EXACT HR+ camera (Siemens/CTI, Knoxville, Tennessee), which enables the acquisition of 63 contiguous planes of data with a distance of 2.46 mm, resulting in a total axial field of view of 155 mm. Subjects were positioned in the scanner with the head fixated and a venous catheter for tracer injections was inserted. A 10-minute transmission scan was performed using three retractable germanium (^{68}Ge) rotating line sources. The tracer [^{11}C]-DASB was administrated as a rapid bolus injection and image acquisition started simultaneously. Data were acquired in three-dimensional (3D) mode during 60 min (1 × 60 s, 4 × 30 s, 3 × 60 s, 4 × 120 s, 2 × 180 s, 8 × 300 s frames).

2.4. Calculation of [^{11}C]-DASB regional binding potentials

Dynamic images were reconstructed using ordered subsets expectation maximization with six iterations, eight subsets and a 4 mm Hanning filter. Motion correction was applied to the dynamic data using Voiager (GE Healthcare, Uppsala, Sweden). The binding potential (BP) for each voxel was calculated using the reference Logan method (Logan et al., 1996). Cerebellum was used as reference region because it only has trace levels of serotonin transporters (Kish et al., 2005). The region was defined on a PET image summed over of all 22 frames using the PVElab software (Svarer et al., 2005), an observer independent approach for automatic generation of regions of interest. The analysis was performed in the time window 40–60 min post bolus injection and BP was estimated as the distribution volume ratio minus one. The BP of [^{11}C]-DASB is highly reproducible (Frankle et al., 2006; Kim et al., 2006) and could therefore be assumed to be stable between the time of PET-scanning and fear conditioning.

2.5. Regions of interest (ROIs)

Anatomically a priori defined ROIs included fear circuit areas (Sehlmeyer et al., 2009) comprising the amygdala, the anterior cingulate cortex (ACC), and the insula. The left and right amygdala ROIs were defined as a 5 mm radius sphere centered on the center co-ordinate (left amygdala: −22, −4, −15; right amygdala: 22, −4, −15) of the statistical maxima of the CS+ vs. CS− comparison in previous human neuroimaging studies on differential fear conditioning (Buchel et al., 1998; Carter et al., 2006; Cheng et al., 2006, 2007; Knight et al., 2004; LaBar et al., 1998; Milad et al., 2007; Petrovic et al., 2008; Phelps et al., 2004; Straube et al., 2007; Tabbert et al., 2005, 2006, 2011). The insula and ACC ROIs were defined in MNI space using the Automated Anatomical Labeling (AAL) library from the Wake Forest University (WFU) Pickatlas (Maldjian et al., 2003). ROIs were defined bilaterally as we did not have any hypothesis regarding laterality.

Rhodes et al. (2007) have previously used the lingual gyrus as a control region to assess the specificity of correlations between amygdala [^{11}C]-DASB BP and amygdala responses to emotional facial expressions. Therefore, we also here used the lingual gyrus to evaluate the specificity of the correlations between fear conditioning and [^{11}C]-DASB BP in the fear circuit. No correlation between [^{11}C]-DASB BP and fear conditioning was expected in the lingual gyrus. The lingual gyrus was also defined using the AAL library within WFU PickAtlas software. In total, five ROIs were investigated: right amygdala, left amygdala, bilateral ACC, bilateral insula and bilateral lingual gyrus.

2.6. Preprocessing of [^{11}C]-DASB BP images

The [^{11}C]-DASB BP images were coregistered to the summation image of all 22 [^{11}C]-DASB frames for each subject. The summation images were then normalized to the SPM PET template using affine transformation, and the transformation parameters were applied to the BP images resulting in MNI normalized BP images. The BP images were subsequently smoothed with an 8 mm isotropic Gaussian kernel.

2.7. Statistical analysis

[^{11}C]-DASB BP images were entered into a regression model in SPM8 (Wellcome Department of Cognitive Neurology, University College London, www.fil.ion.ucl.ac.uk) with the difference in SCR to the CS+ relative to the CS− used as covariate of interest. Because of our *a priori* prediction of an inverse relation between [^{11}C]-DASB binding potential and fear conditioning in the amygdala, we used a probability level of $P < 0.05$ corrected for multiple comparisons within the ROI using family

wise error (FWE) correction as our criterion for statistical significance. For nodes in the extended fear network we used a more conservative criterion to correct for multiple comparisons. The program 3dClustSim from the AFNI library (afni.nimh.nih.gov) was used to calculate a minimum cluster extent with the joint peak threshold set to $P < 0.001$ and the cluster extent threshold to $P < 0.05$. The volume of the bilateral ACC mask was 2713 voxels (21,704 mm^3), that of the bilateral insula 3628 voxels (29,024 mm^3), and that of the bilateral lingual gyrus was 4379 voxels (35,032 mm^3). These volumes resulted in an estimated minimum cluster size of 6 voxels (48 mm^3) for the ACC mask 11 voxels (88 mm^3) for the insula mask, and 19 voxels for the lingual gyrus mask (152 mm^3).

All analyses described above were performed also for SCR to CS+ only and revealed a similar pattern supporting that the excitatory aspects of fear conditioning reflected in CS+ responses account for the effect, rather than stemming from any inhibitory CS− influences.

3. Results

The autonomic measure of fear conditioning demonstrated successful conditioning ($t_{13} = 3.24$; $P = .006$) as shown by the increased responding to the fear cue (CS+) as compared to the control cue (CS−) (Fig. 1A).

We observed a negative correlation between right amygdala [^{11}C]-DASB BP and fear conditioning (*MNI-coordinates:* 18, −6, −16; $Z = 2.57$; $k = 2$, $P = 0.03$ FWE-corrected) indicating that enhanced serotonin transporter availability predicted attenuated fear conditioning (see Fig. 1B, C). In addition, increased [^{11}C]-DASB uptake in the dorsal ACC (*MNI-coordinates:* −6, 36, 22; $Z = 3.60$; $k = 98$, $P < 0.001$ cluster-corrected) and the anterior insula (*MNI-coordinates:* 36, 14, 14; $Z = 3.21$; $k = 56$, $P = 0.001$ cluster-corrected) predicted attenuated fear conditioning (Fig. 2A, B). To test whether these negative correlations were robust and not simply driven by extreme values, we extracted the BP values for the voxel with the statistical maximum in each ROI and computed the Spearman's rank correlation between each ROI and the fear conditioning index. The rank correlations were all significant (ACC: $r = -0.74$, $p = 0.003$; amygdala: $r = -0.66$, $p = 0.01$; insula: $r = -0.80$, $p = 0.0009$).

To determine the specificity of the findings in the fear circuitry, we related fear conditioning to [^{11}C]-DASB BP in the occipital cortex where no correlation was expected. As predicted, no association was found between the autonomic index of fear conditioning and BP in this area ($P > 0.05$).

4. Discussion

Our imaging results are consistent with previous animal data (Burghardt et al., 2007) supporting that extracellular serotonin facilitates fear conditioning. The peak correlations between the autonomic fear conditioning index and [^{11}C]-DASB BP were located in the dorsal part of the ACC, the anterior part of the insula and in the basolateral amygdala. Because conditioned fear memory in animals is dependent on amygdala plasticity (LeDoux, 2000), and since the human amygdala is involved both in fear memory formation and expression (Agren et al., 2012; Furmark et al, 1997), our results are consistent with the notion that serotonin is a determinant of fear learning in humans.

Our findings could aid in understanding risk for developing experience-induced anxiety disorders such as post-traumatic stress disorder (PTSD). Previous studies have found that decreased serotonin transporter (5-HTT) availability is associated with increased levels of anxiety in individuals with PTSD (Murrough et al., 2011). The reduced serotonin transporter availability in the amygdala of patients with PTSD (Murrough et al., 2011) could indicate that low 5-HTT availability is a risk factor for, or an effect of, the disorder. Our observation that 5-HTT availability predicts fear conditioning in a non-PTSD sample favors the risk marker notion and complements previous findings that the short allele of the human 5-HTT gene regulatory polymorphism (5-HTTLPR) is associated with enhanced fear conditioning (Garpenstrand et al., 2001; Lonsdorf et al., 2009) as well as enhanced trauma induced anxiety (Xie et al., 2009). The short 5-HTTLPR allele is associated with less effective serotonin transporter function (Lesch et al., 1996). The previous findings of enhanced fear conditioning and trauma induced anxiety in carriers of the short allele are therefore in line with our present observation of enhanced fear conditioning in participants with lower [^{11}C]-DASB BP. 5-HTTLPR is not only associated with increased risk of developing anxiety disorders but has also been shown to influence the response to psychological treatment (Eley et al., 2012; Knuts et al., 2014). This may suggest that the serotonin transporter is important for neural plasticity related to fear memory in general.

A limitation of this study is that the time of assessment of the PET-data and the fear conditioning data differed by four months. The BP of [^{11}C]-DASB could thus have changed between the time of PET-scanning and fear conditioning. Several studies have found that [^{11}C]-DASB BP is stable over short time periods (Frankle et al., 2006; Kim et al., 2006). It however needs to be established whether it remains stable over several months, as in the present study. Another limitation is the relatively limited number of participants. Therefore, the findings need to be replicated in order to confirm the validity of the results.

Many facets of the neural mechanisms mediating the relation between 5-HTT availability and fear conditioning remain to be uncovered, but permanent 5-HTT deletion can induce morphologic changes in amygdala connectivity over the course of development that in turn influence fear memories (Karpova et al., 2011; Wellman et al., 2007). Conversely, overexpression of 5-HTT in the mouse brain impairs fear conditioning and the hemodynamic response to fear cues in the

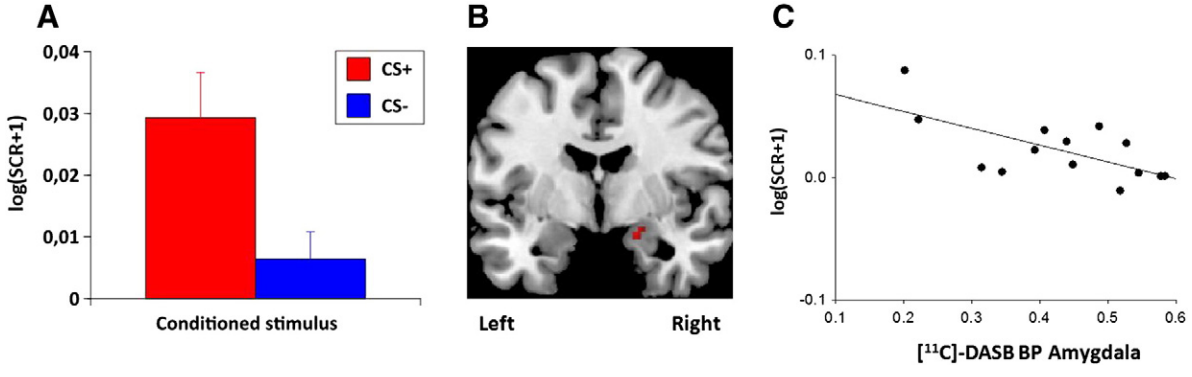

Fig. 1. Serotonin transporter availability in the basolateral amygdala predicts fear conditioning. A. Conditioned autonomic responses to the fear cue predicting shock (CS+) were greater than to the control cue (CS−). B. Statistical parametric map illustrating the correlation between right amygdala serotonin transporter availability and fear conditioning, indexed by the difference in skin conductance responses (SCRs) to CS+ subtracted from CS−. C. Fear conditioning plotted against [^{11}C]-DASB binding potential in the right amygdala. The autonomic nervous system measure of fear is the difference score between SCRs to the fear cue and the control cue. Error bars are standard error of means. MNI, Montreal Neurological Institute.

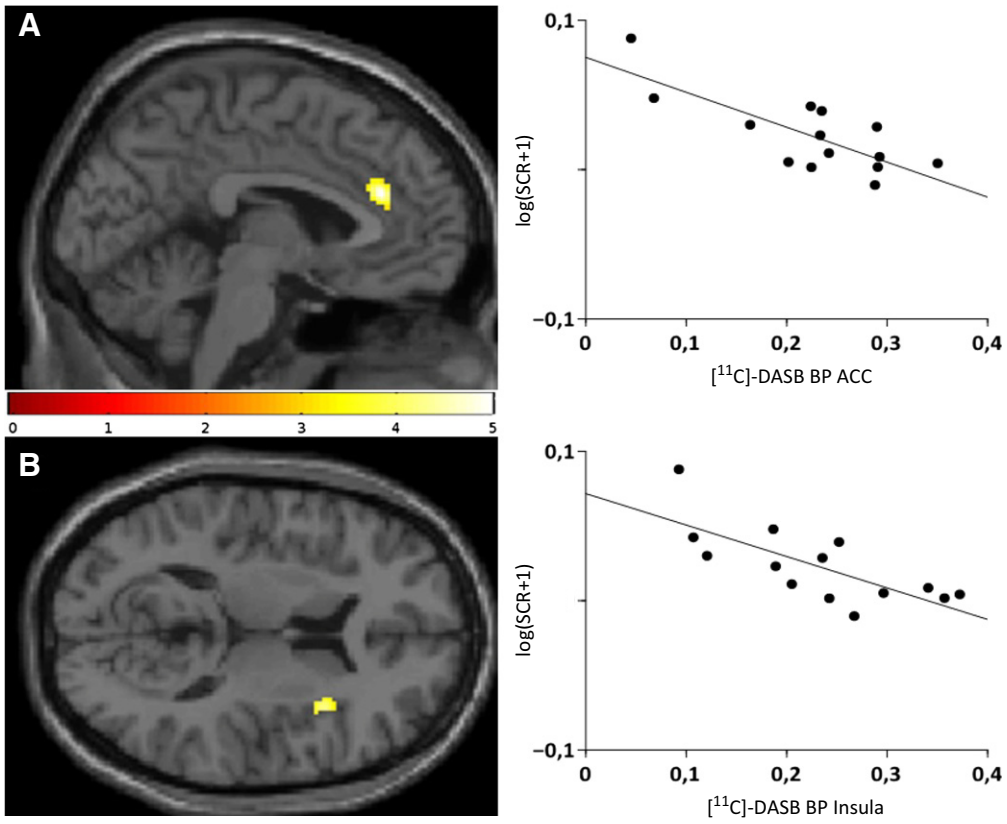

Fig. 2. Serotonin transporter availability in the fear circuitry predicts fear conditioning. Negative correlations between [^{11}C]-DASB binding potential and conditioned autonomic fear responses (CS+–CS−) were evident in A) the dorsal anterior cingulate cortex and B) the anterior insula cortex. CS+, reinforced conditioned stimulus; CS−, unreinforced control stimulus.

amygdala (Barkus et al., 2014). These studies indicate that permanent changes of 5-HTT expression alter fear memory formation. More transiently, 5-HTT blockade can alter serotonergic transmission and modulate neurotransmitters central to emotional learning including glutamate and gamma-aminobutyric acid (Asan et al., 2013), leaving open the possibilities that our findings reflect serotonergic modulation of brain morphology (Wellman et al., 2007) or basic inhibitory and excitatory neurotransmission (Asan et al., 2013). We conclude that serotonergic modulation of fear circuitry activity in the brain is inherently involved in fear formation and expression.

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