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Valence processing alterations in SAPAP3 knockout mice and human OCD

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ABSTRACT

Abnormalities in valence processing – the processing of aversive or appetitive stimuli – may be an under-recognized component of obsessive-compulsive disorder (OCD). Preclinical rodent models have been critical in furthering pathophysiological understanding of OCD, yet there is a dearth of investigations examining whether rodent models of compulsive behavior show alterations in valence systems congruent with those seen in individuals with OCD. In this study, we sought to assess valence processing in a preclinical rodent model of compulsive behavior, the SAPAP3 knockout (KO) mouse model, and compare our preclinical findings to similar behavioral phenomena in OCD patients. In SAPAP3 KO mice, we used auditory fear conditioning and extinction to examine alterations in negative valence processing and reward-based operant conditioning to examine alterations in positive valence processing. We find that SAPAP3 KO mice show evidence of heightened negative valence processing through enhanced fear learning and impaired fear extinction. SAPAP3 KO mice also show deficits in reward acquisition and goal-directed behavior, suggesting impaired positive valence processing. In OCD patients, we used validated behavioral tests to assess explicit and implicit processing of fear-related facial expressions (negative valence) and socially-rewarding happy expressions (positive valence). We find similar trends towards enhanced negative and impaired positive valence processing in OCD patients. Overall, our results reveal valence processing abnormalities in a preclinical rodent model of compulsive behavior similar to those seen in OCD patients, with implications for valence processing alterations as novel therapeutic targets across a translational research spectrum.

1. Introduction

Neural systems that process valence (i.e., positive and negative affect) are crucial for orchestrating adaptive behavioral responses to individuals, objects, or events with emotional salience. Dysfunction or imbalance of valence processing systems contributes to many psychiatric disorders. Obsessive-compulsive disorder (OCD) (American Psychiatric Association, 2013) is one psychiatric condition in which alterations in both negative and positive valence processing may be characteristic of the disorder (Abramovitch et al., 2014; Apergis-Schoute et al., 2017; Figee et al., 2011; Kumari et al., 2001; Milad et al., 2013; Nielen et al., 2009; Simon et al., 2010; Tolin et al., 2003). Valence processing abnormalities may relate in fundamental ways to the behaviors characteristic of OCD. Overactive threat detection may drive behavioral avoidance and compulsions aimed at mitigating threat or decreasing anxiety (McGuire et al., 2012; Tolin et al., 2003), while deficits in reward processing may impair action-outcome contingency learning (Nielen et al., 2009; Palminteri et al., 2012; Remijnse et al., 2006) and bias OCD patients towards habitual over goal-directed behavior (Gillan et al., 2011, 2014, 2015; Gillan and Robbins, 2014). Furthermore, the proneness to habitual behavior observed in OCD may further be driven by hyperactive negative valence processing (Otto et al., 2013; Schwabe and Wolf, 2009).

Studies examining valence processing alterations in preclinical

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models relevant to OCD are limited. Mouse strains in which specific genetic deletions lead to compulsive-like repetitive behaviors have advanced pathophysiological understanding of OCD (Ahmari, 2016; Proenca et al., 2011; Thompson et al., 2019; Zike et al., 2017). As no well-established risk gene of OCD has been identified, these genetic models provide biological insight into OCD through their robust behavioral and neurobiological similarities to the disorder. One of these well-established models is the SAPAP3 knockout (KO) mouse model, in which the *Sapap3* gene is altered resulting in the loss of *Sapap3* gene expression. The *Sapap3* gene is a postsynaptic density protein expressed at excitatory synapses that interacts with the PSD95 and Shank proteins (Welch et al., 2007). In the SAPAP3 KO mouse model, loss of *Sapap3* gene expression leads to impaired frontostriatal synaptic transmission and excessive and detrimental grooming (Welch et al., 2007). OCD pathology has similarly been tied to dysregulated frontostriatal circuits (Ahmari and Dougherty, 2015; Fineberg et al., 2010; Pauls et al., 2014), suggesting that due to the behavioral and physiological similarities between the SAPAP3 KO model and OCD, understanding valence processing in SAPAP3 mice could further advance translational science relevant to OCD. In addition, to fully understand the translatability of preclinical findings, it may be helpful to determine whether phenomena identified in preclinical rodent models are concordant with readily measurable valence processing alterations in human OCD patients. Furthermore, measurable alterations of both positive and negative valence processing in OCD patients could have additional utility through serving as markers of illness severity, targets for therapeutic intervention, or as predictors of treatment response.

In this study, we sought to examine valence processing alterations in the SAPAP3 KO mouse model of compulsivity. In SAPAP3 KO mice, we examined alterations in valence processing using a classical auditory fear conditioning and extinction paradigm (negative valence) as well as a reward-based operant conditioning paradigm (positive valence). In addition, we sought to validate the translatability of our preclinical findings by examining valence processing in OCD patients. While an extensive literature has studied both positive and negative valence processing in human OCD patients, using symptom provocation, extinction learning, or instrumental learning paradigms (Figee et al., 2011; Geller et al., 2017, 2019; McGuire et al., 2016; Milad et al., 2013; Simon et al., 2010), we employed a standardized and validated emotional faces task, easily delivered and performed in a single sitting, to simultaneously assess potential negative and positive valence processing differences. Although many studies have explored processing of emotional face stimuli in OCD, particularly with reference to disgust or identification of emotional expression generally (Corcoran et al., 2008; Daros et al., 2014; Parker et al., 2004; Sprengelmeyer et al., 1997), we specifically assessed behavioral responses to faces expressing fear and happiness, given evidence that they potently engage brain regions involved in the processing of threat (negative valence) and reward (positive valence), respectively (Phan et al., 2002). We additionally used a testing paradigm that allowed examination of both explicit (conscious) and implicit (unconscious) processing of emotional face stimuli. We find that SAPAP3 KO mice show consistent trends towards enhanced negative valence processing and impaired positive valence processing, and that human OCD patients show enhanced responsivity to negative valence images and decreased responsivity to positive valence images. Our results support a model of enhanced negative and impaired positive valence processing in OCD, and reveal the translational potential of such positive and negative valence alterations seen in the SAPAP3 KO mouse.

2. Materials and methods

The full methodology for this paper can be found in the **Supplementary Methods**.

2.1. Animals

Male and female SAPAP3 wild-type (WT) and knock-out (KO) mice (B6.129-*Dlgap3tm1Gfng*/J) bred on a C57/BL6 background were used for all experiments (Fear conditioning: 6 WT female, 5 WT male, 5 KO female, 6 KO male; Operant conditioning: 8 WT female, 3 WT male, 6 KO female, and 2 KO male). The compulsive grooming phenotype does not appear in KO mice until 4 months of age, thus all animals were over 120 days old (average age = 234 days old, age range: 151–308 days old). All experiments were conducted in accordance with national guidelines and procedures established by the Institutional Animal Care and Use Committee at the University of California, San Francisco. Different animals were used for fear conditioning and operant conditioning tasks. Please see **Supplementary Methods** section ***Animals*** for more information.

2.2. Rodent behavioral tasks

2.2.1. Auditory fear conditioning and extinction

All fear conditioning and extinction procedures occurred inside standard operant boxes (Med Associates, St. Albans, VT, USA). On the fear conditioning day, after a 2 min baseline period, mice were exposed to 4 tone-shock pairings (30 s, 80 dB, 5 kHz tone; 1 s, 0.5 mA electric shock, tone and shock co-terminate, randomized intertrial interval (ITI): 30–90 s). On fear extinction days 2–6, after a 2 min 30 s baseline, mice were exposed to 4 tone-only presentations (30 s 80 dB 5 kHz tones, randomized ITI: 30–90 s) in a different context from the conditioning context. Due to our interest in auditory fear retrieval and extinction, we significantly changed the context for the extinction days in order to mitigate contextual fear and freezing. FreezeFrame software (Wilmette, IL, USA) was used to perform tone/shock procedures and to automate quantification of freezing behavior. Please see **Supplementary Methods** section ***Auditory Fear Conditioning and Extinction*** for more information.

2.2.2. Goal vs. Habit Lever Press Paradigm

Methods are modified from Gremel et al., (2013) (Gremel and Costa, 2013). Please see **Supplementary Methods** section ***Goal vs. Habit Lever Press Paradigm*** for more information including the details of each training stage. Mice underwent two training sessions daily in two distinct contexts (clear plastic walls vs. black and white striped walls) in Med Associates operant chambers housed in sound attenuation boxes. In the initial phase, mice learned to nosepoke for reward during two days of fixed ratio 1-fixed time 30 (FR1-FT30) training followed by continuous reinforcement 15 (CRF15) training until the criterion of 15 rewards within 60 min two days in a row was reached. This was followed by four days of continuous reinforcement 30 (CRF30) training. Mice underwent FR1-FT30, CRF15, and CRF30 training in each environmental context. Then mice were assessed for differences in goal directed and habit learning using random ratio (RR) training or random interval (RI) training (1 day of RR5/RI15, 2 days of RR10/RI30, 4 days of RR20/RI60). Finally, a devaluation test was performed consisting of two days of non-reinforced probe tests in either valued or devalued conditions in both the RR and RI contexts. Food restriction occurred for the duration of the experiment.

2.3. Human participants

This investigation was carried out in accordance with the Declaration of Helsinki. Stanford University Administrative Panel for the Protection of Human Subjects (Institutional Review Board) approval was obtained for all procedures. Informed consent of the participants was obtained after the nature of the procedures had been fully explained. Male and female participants ages 18 to 65 seeking participation in a clinical trial for OCD were recruited. Participants were required to have OCD as assessed by the structured clinical interview for DSM-5 (SCID-5) (First et al., 2015) with at least moderate symptoms (Yale-Brown

Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989) score >16 and recurrent intrusions >8 h daily) and to not be using psychotropic medication. The Depression Anxiety Stress Scales (DASS) (Crawford and Henry, 2003; Lovibond and Lovibond, 1995), Obsessive Compulsive Inventory-Revised (OCI-R) (Foa et al., 2002) and Yale Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman et al., 1989), which show good psychometric properties, were administered to each participant. All data were obtained at baseline, prior to any experimental clinical intervention. Please see **Supplementary Methods** section ***Human Participants*** for more information.

2.4. Emotion processing tasks

WebNeuro tasks, which have been validated against gold-standard neuropsychological tests assessing equivalent constructs and demonstrate sound psychometric properties (Paul et al., 2005; Silverstein et al., 2007), were used. Subject-level performance was quantified as a z-score with reference to age-, biological sex-, and years of education-matched norms derived from a control norm cohort of n = 1317 (Mathersul et al., 2009; Williams et al., 2009) (see **Supplemental Methods** for detailed description). Tasks used in this study included i) an *explicit emotion processing* task, assessing participants' conscious verbal labeling of emotional face stimuli, and, ii) a subsequent *implicit emotion processing* task assessing the priming (unconscious) effects of emotional expression on participants' performance of an otherwise neutral face recall task. In the explicit emotion processing task, 48 images from a standardized and validated set of emotional face images were pseudorandomly presented for 2 s each, during which participants select, as quickly and accurately as possible, the correct label from a list of emotional expression labels. After an interval of approximately 20 min, during which participants complete unrelated cognitive tasks, participants complete the implicit emotion processing task. Stimuli in the implicit task include the 48 face images presented during the explicit task as well as an additional 48 previously unseen images from the same standardized set. From each simultaneously presented image pair, participants are asked to select, as quickly and accurately as possible, the image they have previously seen. For both the explicit and implicit emotion processing tasks, Z-scores reflected normed performance on measures of accuracy (% correctly labeled expressions, or % correctly recalled faces) and reaction time. Please see Fig. 3A and **Supplementary Methods** section ***Emotion Processing Tasks*** for more information.

2.5. Statistical analysis

For rodent data, normality was tested with D'Agostino & Pearson normality test and parametric and non-parametric tests were used where appropriate. Wilcoxon rank sum test, unpaired *t*-test, Pearson correlation, and two-way repeated measures ANOVA with Sidak's and Tukey's correction for multiple comparisons were used. For the fear conditioning and extinction experiment, mice that did not sufficiently recall the tone-shock association as evidenced by an average of less than 40% freezing to the tone on Day 1 of extinction were excluded from the analysis (5 WT and 2 KO mice excluded).

For human data, non-parametric statistical methods were used throughout, given that the distribution of our participants' age- and gender-normalized z-scores for several explicit and implicit emotional processing measures deviated from the normal distribution per Shapiro-Wilk tests. One-sample Wilcoxon rank sum tests (two-tailed, $\mu = 0$) and Spearman's rank correlation coefficient were used. Given the hypothesis-generating nature of the correlational analyses, p-values are reported without correction for multiple comparisons. Please see **Supplementary Methods** section ***Statistical Analysis*** for more information.

3. Results

3.1. Fear conditioning and extinction task

SAPAP3 KO mice showed significantly increased grooming behavior (Fig. 1A, Wilcoxon Rank Sum Test, p = 0.0014; WT = 11, KO = 11) compared to WT controls, replicating the established phenotype of this model. We next assessed alterations in negative valence processing in SAPAP3 KO mice using a classical auditory fear conditioning paradigm as well as a multi-day fear extinction procedure (Fig. 1B). During fear conditioning, SAPAP3 KO mice showed no differences in freezing during the pre-tone period or tone 1, but showed a significant increase in freezing to tones 2–4 compared to WT mice (Fig. 1C, Two-way Repeated Measures ANOVA, Time x Genotype p = 0.0016, Time p < 0.0001, Genotype p = 0.0001; Sidak's Multiple Comparisons Test, WT vs. KO Pre-Tone p > 0.9999, Tone 1 p = 0.9942, Tone 2 p = 0.0106, Tone 3 p < 0.0001, Tone 4 p = 0.0002; WT = 11, KO = 11). These results demonstrate that SAPAP3 KO mice show enhanced fear learning.

During extinction, there was no difference in freezing between WT and SAPAP3 KO mice during the pre-tone period or during Tones 1–3. However, following the first few tones, WT mice showed significantly lower freezing to the tone compared to SAPAP3 KO mice (Fig. 1D, Two-way Repeated Measures ANOVA, Time x Genotype p = 0.0013, Time p < 0.0001, Genotype p < 0.0001; Sidak's Multiple Comparisons Test, WT vs. KO Pre-Tone p = 0.8080, Tone 1 p = 0.4570, Tone 2 p = 0.9962, Tone 3 p 0.6162, Tone 4 p = 0.0157, Tone 5 p = 0.5548, Tone 6 p = 0.001, Tone 7 p = 0.0024, Tone 8 p = 0.0033, Tone 9 = 0.0035, Tone 10 p = 0.0883, Tone 11 p = 0.0002, Tone 12–13 p < 0.0001, Tone 14 p = 0.0003, Tone 15–16 p < 0.0001, Tone 17 p = 0.0034, Tone 18 p < 0.0001, Tone 19 p = 0.0016, Tone 20 p < 0.0001; WT = 11, KO = 11). WT mice significantly decreased their freezing to the tone from early to late extinction, which indicates successful fear extinction. Conversely, SAPAP3 KO mice did not show a significant difference in freezing between early and late extinction, suggesting impaired ability to extinguish fear (Fig. 1E, Two-way Repeated Measures ANOVA, Time x Genotype p = 0.0119, Time p < 0.0001, Genotype p < 0.0001; Sidak's Multiple Comparisons Test, WT Tone 1 vs. Tone 20 p < 0.0001, KO Tone 1 vs. Tone 20 p = 0.2612; WT = 11, KO = 11). This general increase in freezing behavior in the SAPAP3 KO mice was due to an increase in average freezing bout duration across all days of extinction (Fig. 1F, Unpaired T-Test, p = 0.0006; WT = 11, KO = 11) with no difference in the average number of freezing bouts across all days of extinction (Fig. 1G, Wilcoxon Rank Sum Test, p = 0.7348; WT = 11, KO = 11). There were no significant differences in fear conditioning and extinction behavior between males and females of the same genotype (Supplemental Fig. 1). Overall, these results indicate that SAPAP3 KO mice show impaired fear extinction.

3.2. Reward-based operant conditioning task

To assess alterations in positive valence processing, we trained WT and SAPAP3 KO mice on a multi-stage reward-based operant conditioning paradigm (Fig. 2A). WT mice learned the association between nosepoke and reward quickly and then stably maintained nosepoke behavior, whereas SAPAP3 KO mice were much slower at learning nosepoke behavior, with two KO mice never achieving stable performance (Fig. 2B, Supplemental Fig. 2A, Two-way Repeated Measures ANOVA, Genotype x Training Day p < 0.0001, Training Day p < 0.0001, Genotype p < 0.0001; Sidak's multiple comparisons, WT vs. KO Day 1 p = 0.4636, Day 2 p = 0.0004, Days 3–5 p < 0.0001, Day 7 p < 0.0001, Day 9–10 p < 0.0001, Day 12 p < 0.0001, Day 14 p = 0.0010, Day 15 p = 0.0009, Day 17 p = 0.0363; WT = 11, KO = 8). It took SAPAP3 KO mice on average over 3 times as many training days to establish stable nosepoke behavior compared to WT mice (Fig. 2C, Wilcoxon Rank-Sum Test, p = 0.0005; WT = 11, KO = 6). Total grooming duration in the SAPAP3 KO mice did not correlate with the number of rewarded nose

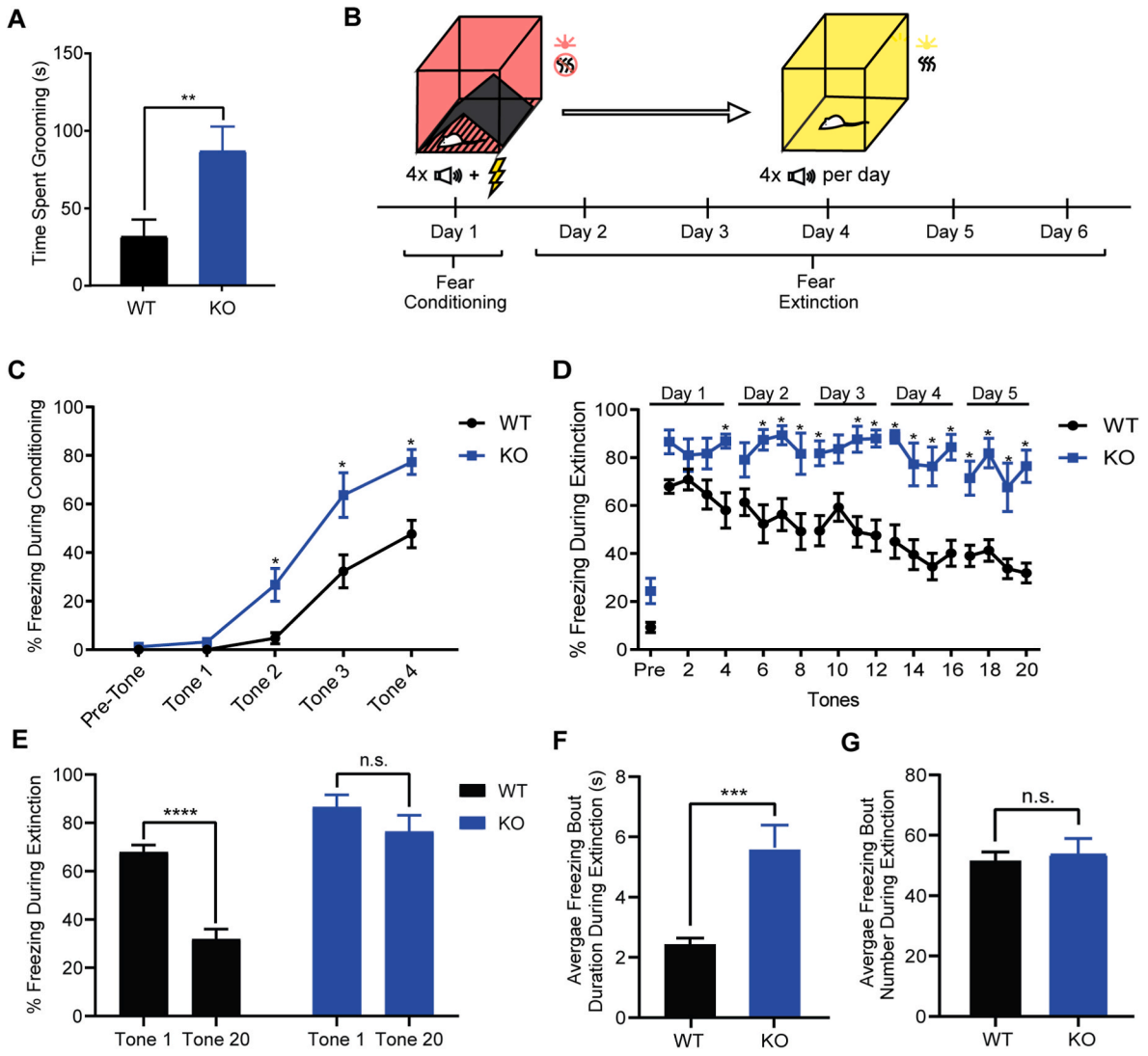

Fig. 1. SAPAP3 KO mice show enhanced fear learning and impaired fear extinction. (A) SAPAP3 KO mice spent significantly more time grooming than WT mice. (B) Schematic for the fear conditioning and extinction procedure. (C) SAPAP3 KO mice froze to the tone significantly more than WT mice during tones 2–4 of fear conditioning. (D) SAPAP3 KO mice froze to the tone significantly more than WT mice during days 2–5 of fear extinction. (E) SAPAP3 WT mice significantly decreased their freezing from the first to the last tone presentation during extinction while SAPAP3 KO mice did not show a significant decrement in freezing across extinction. (F) SAPAP3 KO mice had a significantly increased average freezing bout duration across extinction compared to WT mice. (G) SAPAP3 KO mice showed no difference in average freezing bout number across extinction compared to WT mice. * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$, **** = $p \leq 0.0001$; stars in graphs 1C and 1D convey significance but not level of significance.

pokes during training, suggesting that deficits in nose poke behavior in the SAPAP3 KO mice were not a result of excessive time spent over-grooming (Fig. 2D, Pearson correlation, $r^2 = 0.08398$, $p = 0.4863$). SAPAP3 WT mice also showed no significant correlation between total grooming duration and total rewarded responses during training (Supplemental Fig. 2B). After examining differences in acquisition of nose-poke behavior, we next examined how nosepoke behavior was maintained in each genotype under two different reinforcement schedules, one biasing for habit formation (random interval), and one for goal-directed behavior (random ratio) (Gremel and Costa, 2013). SAPAP3 KO mice continued to earn a high level of rewards under the reinforcement schedule that promotes habitual responding, but their ability to earn reward greatly diminished under the reinforcement schedule that promotes goal-directed responding (Fig. 2E, Two-way Repeated Measures ANOVA, Genotype x Training Day $p < 0.0001$, Training Day $p < 0.0001$, Genotype $p < 0.0001$; Tukey's multiple comparisons, Days 1–4 of CRF30 Training and Day 1 of RR5/RI15 Training WT RR vs. KO RR $p > 0.9999$, WT RI vs. KO RI $p > 0.9999$, and KO RR vs. KO RI $p > 0.9999$, Day 1 of RR10/RI30 Training WT RI vs. KO RR $p = 0.0005$, WT RR vs. KO RR $p = 0.0212$, and KO RR vs. KO RI $p = 0.0598$, Day 2 of RR10/RI30 training WT RI vs. KO RR $p = 0.0005$, WT RR vs. KO RR $p = 0.0059$, and KO RI vs. KO RR $p = 0.003$, for each RR20/RI60 Training Days 1–4 WT RI vs. KO RR $p < 0.0001$, WT RR vs. KO RR $p < 0.0001$, and KO RI vs. KO RR $p < 0.0001$; WT = 11, KO = 6). SAPAP3 KO mice nosepoked significantly less than SAPAP3 WT mice during both random ratio and random interval training (Supplemental Fig. 2C). Finally, we performed a devaluation test to assess goal-directed or habitual responding in both the random ratio and random interval contexts. We found that SAPAP3 WT mice showed devaluation in the random ratio context indicative of goal-directed responding while SAPAP3 KO mice did not, further suggestive of disrupted goal-directed behavior in the SAPAP3 KO mice (Fig. 2F, Two-Way Repeated Measures ANOVA, Genotype x Condition $p = 0.3534$, Genotype $p > 0.9999$, Condition $p = 0.005$; Sidak's multiple comparisons, WT Valued vs. WT Devalued $p = 0.0036$, KO Valued vs. KO Devalued $p = 0.3198$; WT = 11, KO = 5). Both SAPAP3 WT and SAPAP3 KO mice did not devalue in the random interval context indicative of

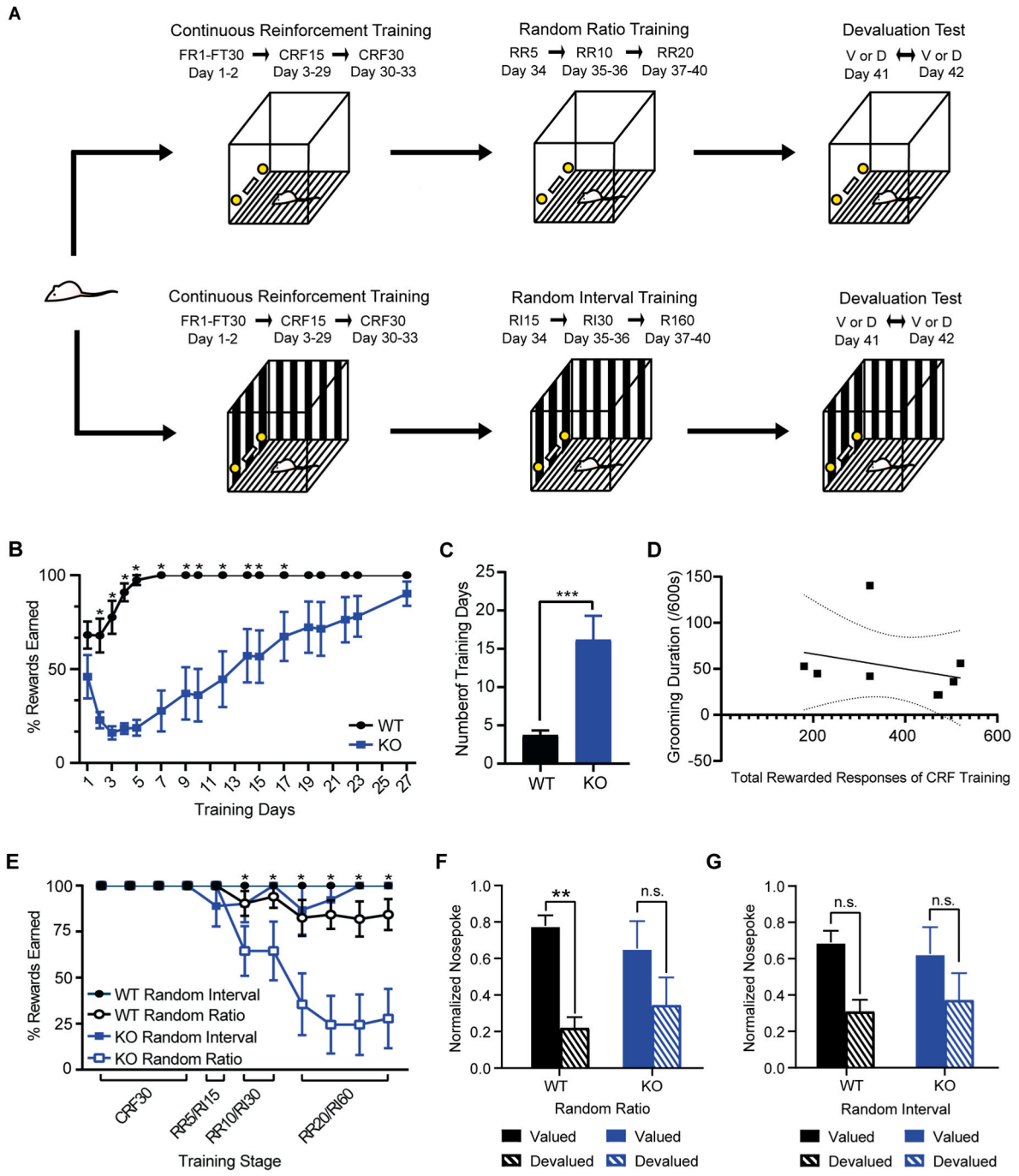

Fig. 2. SAPAP3 KO mice show impaired acquisition of reward learning and goal-directed behavior. (A) Schematic for operant conditioning procedure. Mice were counterbalanced across experimental context and nosepoke side (i.e. for mouse 1 the active nosepoke hole was the left hole in the clear plastic environmental context while the right hole was the active nosepoke hole in the striped environmental context, but this condition was reversed for mouse 2). (B) Learning curve for the acquisition of CRF15 nosepoke behavior on days for which both WT and KO mice received training time. (C) KO mice took significantly longer than WT mice to achieve stable nosepoke behavior for reward during CRF15 training. (D) Total grooming duration in KO mice did not significantly correlate with total rewarded nose poke responses during CRF training. (E) KO mice struggled engaging in the goal-directed nosepoke reward schedule (RR), but did not have difficulty earning rewards under a habit-promoting nosepoke reward schedule (RI). (F) WT mice devalued in the random ratio context while KO mice did not, indicative of impaired goal-directed behavior in the KO mice. (G) Both WT and KO mice did not devalue in the random interval context indicative of habitual responding. FR, fixed ratio; FT, fixed time; CRF, continuous reinforcement; RR, random ratio; RI, random interval; V, valued; D, devalued; * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, **** = $p < 0.0001$; stars in graphs 2B and 2E convey significance but not level of significance.

habitual responding in both genotypes in this context (Fig. 2G, Two-Way Repeated Measures ANOVA, Genotype x Condition $p = 0.6510$, Genotype $p < 0.0001$, Condition $p = 0.0355$; Sidak's multiple comparisons, WT Valued vs. WT Devalued $p = 0.0668$, KO Valued vs. KO Devalued $p = 0.4649$; WT = 11, KO = 6). These data indicate that SAPAP3 KO mice have a learning deficit under positive reward conditions with difficulties both in acquiring positive-reinforced behaviors and in maintaining goal-directed responding for rewards.

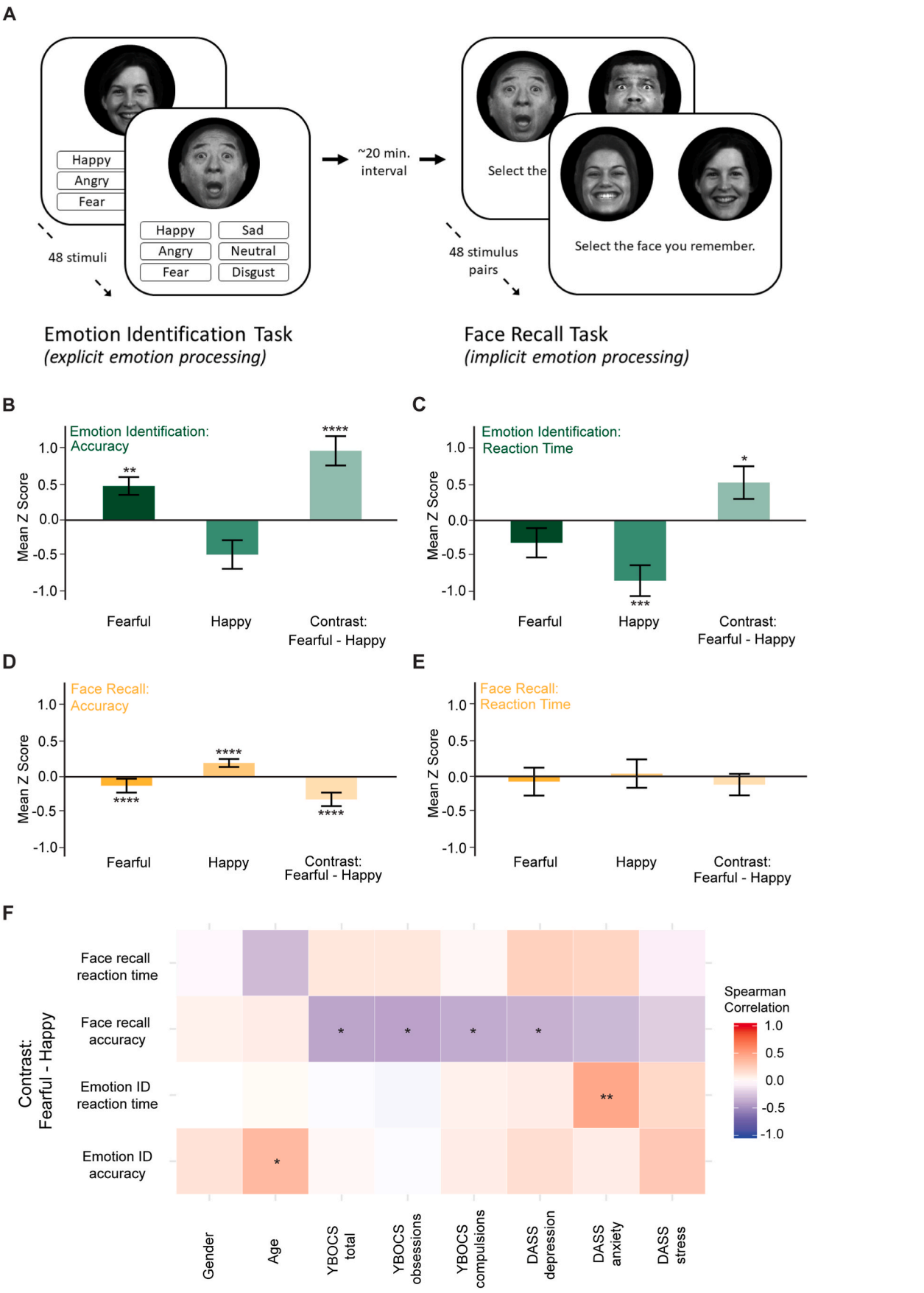

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Fig. 3. Explicit and implicit emotion processing tasks schematic and results. (A) Schematic of the emotional faces paradigm including first an 'explicit' processing task (Emotion Identification Task) in which participants are invited to select the label corresponding to the emotion expressed by each of a series of single face stimuli, and, after an approximately 20 min delay, an 'implicit' emotion processing task (Face Recall Task), in which participants are shown paired emotional face stimuli – including one stimulus used previously in the Emotion Identification Task and one novel stimulus with similar emotional expression – and asked to select the face they had seen previously. *Explicit processing task:* relative to a normative population, (B) OCD patients more accurately identify facial expression of fear, and show bias towards more accurate identification of fearful relative to happy expression. (C) OCD patients more slowly identify facial expression of happiness, and show bias towards more rapid identification of fearful relative to happy expression. *Implicit emotion processing task:* relative to a normative population, (D) OCD patients less accurately recall faces expressing fear, and more accurately recall faces expressing happiness, with negatively biased recall accuracy for faces expressing fear relative to happiness. (E) OCD patients do not differ in speed of face recall, nor is speed of recall biased by the presence of fearful relative to happy expression. (F) Correlations between demographic and clinical variables and fearful vs. happy expression bias on normalized measures of speed and accuracy for both emotion identification (explicit emotion processing) and face recall (implicit emotion processing) tasks. Error bars show standard error of the mean. * = $p \leq 0.05$, ** = $p \leq 0.01$, *** = $p \leq 0.001$, **** = $p \leq 0.0001$.

3.3. OCD patient sample

N = 42 individuals with OCD met eligibility criteria for clinical study participation and were assigned to complete the emotion processing tasks. One participant subsequently elected to pursue outside treatment and was withdrawn prior to task completion, thus data was obtained for N = 41 individuals with OCD. Demographic and clinical characteristics of the sample are described in Table 1. Average total Y-BOCS score was 26.1 ($s = 4.7$) indicating moderate-to-severe symptoms of OCD. Average depression scale score on the DASS was 13.0 ($s = 9.8$) indicating a mild-to-moderate level of depressive symptoms.

3.4. Explicit emotion processing task

We employed a standardized and validated emotional faces task to assess both explicit and implicit emotional processing in OCD patients (Fig. 3A). For explicit emotional processing, compared to control reference norms, OCD participants were significantly more accurate at identifying fearful expressions and non-significantly less accurate at identifying happy expressions, with a difference score (fearful - happy) representing a bias towards accuracy for fearful faces (Fig. 3B, Wilcoxon Rank Sum Test, fearful: mean z = 0.47 ± 0.12, p = 0.001, happy: mean z = −0.49 ± 0.20, p = 0.09, fearful - happy mean z difference = 0.96 ± 0.20, $p < 0.001$). OCD patients were slower in response to both fearful and happy faces than the control reference norms, but this difference was statistically significant only for happy faces (Fig. 3C, Wilcoxon Rank Sum Test, fearful: mean z = −0.31 ± 0.20, p = 0.14; happy: mean z = −0.84 ± 0.21, $p < 0.001$). The difference score for explicit identification reaction times (fearful-happy) suggests a relative acceleration of response to fearful versus happy faces (Fig. 3C, Wilcoxon Rank Sum Test, fearful - happy mean z difference = 0.53 ± 0.23, p = 0.025). Overall, these results indicate that on this assessment of explicit, conscious emotion processing, OCD patients respond more effectively to negative versus positive valence stimuli, with both relatively greater accuracy and speed.

Table 1
OCD patient demographic and clinical variables. Variables collected include gender, race/ethnicity, co-morbidities, and clinical measures such as the Yale Brown Obsessive Compulsive Scale (Y-BOCS) and the Depression Anxiety Stress Scales (DASS). The average Y-BOCS score indicates that enrolled patients had moderate-to-severe symptoms of OCD.

OCD Patient Demographic and Clinical Variables	*N*=41
Age, *mean (range, ± SD)*	
	35.4 (19–58, ±10.8)
Gender[a], *n* (%)	
Female	11 (26.8)
Male	30 (73.2)
Race/Ethnicity[a], *n* (%)	
White, non-hispanic	26 (63.4)
Hispanic	6 (14.6)
Asian	3 (7.3)
Multiracial	6 (14.6)
DSM-5 co-morbidity (current), *n* (%)	
other OCRD	7 (17.1)
depressive disorder	11 (26.8)
anxiety disorder	10 (24.4)
ADHD	6 (14.6)
Other[b]	14 (34.1)
Clinical measures. *mean (range, ± SD)*	
Y-BOCS total	26.1 (17–36, ±4.7)
Y-BOCS obsessions subscale	13.0 (6–18, ±2.6)
Y-BOCS compulsions subscale	13.2 (7–18, ±2.5)
DASS-D	13.0 (0–38, ±9.8)
DASS-A	9.1 (0–40, ±7.8)
DASS-S	17.2 (0–34. ± 8.0)

[a] Self-asserted.
[b] 'Other' includes somatic symptom disorder (n = 4), sleep-wake disorder (n = 4), posttraumatic stress disorder (n = 3), substance use disorder (n = 2), intermittent explosive disorder (n = 1). SD - standard deviation; DSM-5 - Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; OCRD -obsessive-compulsive and related disorder; ADHD - attention deficit hyperactivity disorder; Y-BOCS - Yale-Brown Obsessive Compulsive Scale; DASS Depression Anxiety Stress Scales; -D - depression; -A - anxiety; –S - stress.

3.5. Implicit emotion processing task

Relative to control reference norms, OCD participants were significantly less accurate for face recall when influenced implicitly by fearful expression and more accurate for recall when influenced implicitly by happy expression (Fig. 3D, Wilcoxon Rank Sum Test, fearful: mean z = −0.12 ± 0.10, $p < 0.0001$, happy: mean z = 0.19 ± 0.06, $p < 0.0001$). The difference score (the contrast of scores for the implicit influence of fearful minus happy faces) suggests that there is an implicit interference of fear on face recall, relative to the implicit facilitation of happiness, with a small to moderate effect size (Fig. 3D, Wilcoxon Rank Sum Test, fearful - happy mean z difference = −0.32 ± 0.10, $p < 0.0001$). OCD patients did not differ from control reference norms in the implicit influence of fearful or happy expression on the reaction time for face recall, nor on the contrast measure of difference for the implicit influence of fearful minus happy expression (Fig. 3E, Wilcoxon Rank Sum Test, fearful: mean z = −0.07 ± 0.20, p = 0.53; happy: mean z = 0.04 ± 0.20, p = 0.46, fearful - happy mean z difference = −0.11 ± 0.15, p = 0.38). Overall, these results suggest that negative relative to positively valenced stimuli interfere with the performance on a simple recall task in OCD patients even when the influence of these stimuli is implicitly processed.

3.6. Correlations with clinical and demographic variables

To explore whether biases in negative vs. positive valence processing corresponded to clinical phenomena in OCD patients, we assessed correlations between fearful–happy difference measures and demographic and clinical measures. The degree of difference in explicit emotion identification accuracy for fearful vs. happy faces was positively correlated with participant age, though not with any clinical measure (Fig. 3F, Spearman's rank correlation coefficient, emotion ID accuracy x participant age: rho = 0.37, p = 0.018). The degree of bias towards faster reaction times to fearful stimuli in the explicit emotion identification task correlated positively with scores for the Anxiety subscale of

the DASS, but was not correlated significantly with other clinical or demographic variables (Fig. 3F, Spearman's rank correlation coefficient, emotion ID reaction time contrast x DASS anxiety: rho = 0.46, p = 0.003). For the implicit emotion processing task, the bias towards decreased recall accuracy for fearful relative to happy faces correlated with OCD severity by Y-BOCS (including component subscales) as well as with the Depression subscale of the DASS such that greater symptoms on these clinical measures were associated with more potent interference on face recall by fearful relative to happy expression (Fig. 3F, Spearman's correlation coefficient, face recall accuracy contrast x Y-BOCS: rho = −0.38, p = 0.015; implicit negative bias x DASS depression: rho = −0.32, p = 0.04). The correlation between negative bias in face recall accuracy and Y-BOCS remained significant even when controlling for DASS depression ($rho_{partial}$ = −0.34, p = 0.031). Overall, these results suggest that while subjective anxiety may be associated with faster explicit (conscious) reactivity to negative versus positive valence, clinical OCD symptoms may be associated with greater implicit (non-conscious) impact of negative versus positive valence on other forms of information processing. To assess whether specific subpopulations of OCD participants might demonstrate distinct alterations in negative vs. positive valence processing, we assessed for correlations between subscales of the OCI-R and our fearful–happy difference measures (Supplemental Table 1). No correlations met the threshold for statistical significance.

4. Discussion

We uncovered key alterations in positive and negative valence processing in a preclinical rodent model of compulsive behavior, the SAPAP3 KO mouse model, and, using distinct valence-processing paradigms, found concordant valence processing abnormalities in OCD patients. In the rodent model, we found that SAPAP3 KO mice showed evidence of enhanced fear learning, impaired fear extinction, impaired acquisition of reward learning, and impaired goal-directed behavior. OCD patients were found to have speeded and more accurate identification of fearful compared to happy facial expressions and a greater implicit influence of fear versus happiness on an otherwise neutral face recall task. Overall, our results suggest that the SAPAP3 KO mouse model shows trends toward heightened negative valence processing and impaired positive valence processing similar to valence alterations seen in OCD patients.

SAPAP3 KO mice show enhanced sensitivity to negative valence. While SAPAP3 KO mice showed both enhanced fear learning and impaired fear extinction, only impairments in fear extinction have been consistently found in OCD patients (Geller et al., 2017, 2019; McGuire et al., 2016; Milad et al., 2013). This suggests that studying fear extinction impairments in the SAPAP3 KO mouse model might hold more clinical relevance to OCD than studying enhancements in fear learning. In regards to positive valence processing, SAPAP3 KO mice showed impairments in the acquisition of reward learning. Previous studies in SAPAP3 KO mice utilizing operant tasks have found mixed results with some studies reporting learning deficits while others do not (Ehmer et al., 2020a, 2020b; Hadjas et al., 2019; Manning et al., 2019). However, studies not reporting learning deficits differed in key variables from our study including in the age of the animal used and the phase of the light cycle in which the study was run which could critically contribute to differences in the results seen. Interestingly, OCD patients have also been reported to show impairments in the acquisition of instrumental learning tasks (Nielen et al., 2009; Palminteri et al., 2012; Remijnse et al., 2006). However, these acquisition abnormalities have also been found in some but not all studies (Gillan et al., 2011, 2015), which has been attributed to differences in medication status (Palminteri et al., 2012).

Our study also revealed that SAPAP3 KO mice have impaired goal-directed learning and intact habit learning. SAPAP3 KO mice earned significantly less rewards under the goal-directed nose-poke schedule (RR) and failed to devalue the reward. Instead there was habitual-like responding under devaluation for both RI and RR contexts for the SAPAP3 KO mice. This is in contrast to another study that demonstrated SAPAP3 KO mice had increased goal-directed behavior under RR and RI conditions (Ehmer et al., 2020b). However, reliance on habit-like responding is supported by other studies including failure to devalue under the RI context (Hadjas et al., 2019) as well as a deficit in reversal learning (Manning et al., 2019). This is in alignment with studies that have shown that OCD patients not only show impaired goal-directed behavior, but also excessive habit formation (Gillan et al. 2011, 2014, 2015; Gillan and Robbins 2014).

In OCD patients, the profile of response to fearful versus happy expressions we observed is indicative of a negative valence bias. Previous studies of facial emotion processing in OCD have largely focused on whether OCD patients have deficits in identifying symptom-congruent expressions of disgust and have yielded mixed results (Buhlmann et al., 2004; Corcoran et al., 2008; Parker et al., 2004; Rector et al., 2012; Sprengelmeyer et al., 1997). Meta-analysis of these and other studies of facial emotion processing in OCD suggests a general deficit in identification of facial emotion (Daros et al., 2014), however these studies have not generally explored valence-specific effects or contrasts and have typically assessed patients taking psychotropic medication, whereas antidepressant medication has been shown to alter processing of emotional expressions in individuals with OCD (Lochner et al., 2012) and with depression (Harmer et al., 2009). Other established behavioral assessments of negative valence processing, specifically tests of attentional bias such as the emotional stroop or dot-probe task, characteristically show attentional bias towards threat stimuli in anxiety disorders. Translational animal models of ambiguous cue interpretation similarly suggest that stress conditions lead to negative bias (Enkel et al., 2010; Harding et al., 2004; Papciak et al., 2013). At the same time, in human OCD patients, tests of attentional bias have produced equivocal findings (Morein-Zamir et al., 2013; Schneier et al., 2016; Summerfeldt and Endler, 1998). The inclusion of both explicit and implicit emotion processing measures is a strength of our study, and our observation that anxiety symptoms and OCD symptoms show distinct patterns of correlation with explicit versus implicit measures may help clarify potential differences in negative valence processing between OCD and anxiety disorders.

It is important to note that differences in task design limit the parallels that can be drawn across tasks. While our negative valence paradigm involved fear conditioning which relies on associative learning, our positive valence paradigm involved a reward-based operant conditioning task which relies on both associative and instrumental learning. In addition, the clinical study is distinct from the animal tasks in that the rodent-based assays involved learning associations between conditioned stimuli and rewarding or aversive outcomes while the clinical study involved explicit and implicit emotion processing. Nonetheless, our work supports two new approaches for the study of valence processing abnormalities across a translational spectrum in OCD: the SAPAP3 KO model, and a simple, validated emotional faces paradigm allowing rapid assessment of both explicit and implicit emotional processing in the context of clinical trials. With respect to our emotional faces tasks, the availability of data from a large reference cohort is a strength of this paradigm, however it is a limitation of our study that we did not concurrently assess a healthy control group. Future studies should utilize tasks in which both positive and negative valence processing can be assessed concurrently with similar task designs in both humans and animals. Tasks which interweave trials to obtain reward and trials to avoid punishment through either performing or withholding an action may be particularly apt for increasing the translational potential of findings between human and animal studies (Enkel et al., 2010; Gentry et al., 2016; Guitart-Masip et al., 2012; Harding et al., 2004; Papciak et al., 2013). Similar task designs in both the SAPAP3 mouse model and OCD patients have been used to assess other behavioral processes such as behavioral flexibility and have yielded promising cross-species

findings, highlighting the efficacy of this potential approach (Benzina et al., 2021).

Overall, we have shown that the SAPAP3 KO mouse model of compulsive behavior has enhanced negative valence processing and impaired positive valence processing similar to valence alterations seen in OCD patients. These results suggest that OCD may be characterized by key valence processing alterations and highlight the translational potential of studying valence processing abnormalities in the SAPAP3 KO mouse model. Future work should focus on increasing congruity of tasks between animal and human studies along with clarifying the neurobiological underpinnings of identified valence processing alterations in SAPAP3 KO mice and OCD patients.

5. Contributors

Bridget L. Kajs and Peter J. van Roessel were involved in conceptualization, data curation, formal analysis, writing of the original draft and review and editing. Gwynne L. Davis was involved in conceptualization, data curation, and formal analysis. Leanne M. Williams was involved in conceptualization and formal analysis. Carolyn I. Rodriguez and Lisa A. Gunaydin were involved in conceptualization, funding acquisition, projection administration, supervision, writing of the original draft and review and editing.

Role of the funding source

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Declaration of competing interest

In the last 3 years, Dr. Rodriguez has served as a consultant for Epiodyne Biohaven Pharmaceuticals and and received research grant support from Biohaven Pharmaceuticals and a stipend from APA Publishing for her role as Deputy Editor at The American Journal of Psychiatry. Dr. Williams has served as a scientific advisor for One Mind Psyberguide, a member of the executive advisory board for the Laureate Institute for Brain Research and holds patent 16921388 (Systems and Methods for Detecting Complex Networks in MRI Image Data) unrelated to the present study. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

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