A cross-species assessment of cognitive flexibility in compulsive disorders

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Abstract

Background:

Obsessive-Compulsive Disorder (OCD) is a mental disorder featuring compulsions which are repetitive behaviors performed through rigid rituals. A diminished cognitive flexibility could explain this phenomenological observation. But studies exploring this dimension have yet failed to show consistent deficits in OCD. In animal models of compulsive behavior, too few studies were performed, leaving the question open. The aim of this study was so to assess the involvement of cognitive flexibility in compulsion through a cross-species approach.

Methods:

40 OCD patients, 40 healthy comparison subjects individually matched, 26 C57BL/6J *Sapap3* KO mice and 26 matched wildtype littermates were included in this study. A reversal learning task similar in both species was used to assess cognitive flexibility.

Results:

When considered as homogeneous groups, both OCD patients and KO mice did not significantly differ from their controls. When clinical subtypes were considered, only patients exhibiting checking compulsions were impaired with more trials needed to reach the reversal criterion. In KO mice, a similarly impaired subgroup was identified. For both species, this impairment did not result in a greater perseveration after reversal, but in a greater lability in their responses in reversal condition. Moreover, this impairment did not correlate with the severity of compulsive behaviors.

Conclusions:

Cognitive flexibility is differentially affected across subjects exhibiting compulsive behaviors with only subgroups impaired in a reversal learning task for both species. This impairment manifests itself through a response lability, not a perseveration, in reversal situation. This study is the first to highlight such cross-species results.

Introduction

Since the seminal work of Emil Kraepelin (1) more than a century ago, psychiatric nosology has been based on a categorical approach to mental disorders. However, these diagnostic categories are far from forming homogeneous entities and the latest thirty-year research on their genetic and neurobiological bases has faced the greatest difficulty in identifying specific alterations (2, 3), impeding the development of new treatments (4). This recognition led the way to the dimensional approach spearheaded by the NIMH Research Domain Criteria (RDoC) initiative (5) and based on the identification of intermediate phenotypes (6), closer to the neurobiological/genetic substrate of the disorder than the clinical symptom. In this respect, obsessive compulsive disorder (OCD) which affects 2-3% of the general population (7) and is characterized by obsessions (recurrent, intrusive and unwanted thoughts) often associated with compulsions (rigid, repetitive and ritualized behaviors or mental acts performed in response to the obsessions), should particularly benefit of this paradigm shift since the link between its symptoms and their underlying neurocognitive features remains unclear. Due to the very presence of compulsive behaviors in OCD suggest that one of these core neurocognitive deficit might concern cognitive flexibility (i.e., the ability to flexibly adjust one's behavior to a changing environment (8)). Thus, in line with the RDoC approach, we propose to investigate if a lack of cognitive flexibility could be considered as an intermediate phenotype of compulsive disorders.

Structural and functional imaging in OCD patients point out towards an hyperactivity in the limbic and associative cortical regions as well as their related basal ganglia areas (9) with identified abnormalities in the cortico-basal ganglia circuits (10). Such abnormalities have also been observed in a recent animal model suffering of compulsive behaviors: the *Sapap3* KO mice (11). Indeed these mice have been genetically engineered to lack the SAP90/PSD95-associated protein 3 (*Sapap3*), a postsynaptic scaffolding protein mainly expressed in the striatum (12); leading to a decrease in the cortico-striatal glutamatergic transmission (11, 13). Importantly, these mice show compulsive behaviors characterized by an excessive expression of grooming, which, in wildtype mice, consists in a stereotyped sequence of body-cleaning actions (14), despite negative consequences such as skin lesions. Moreover, these compulsive behaviors can be significantly reduced after chronic administration of fluoxetine as observed in OCD patients (11). For all these reasons, the *Sapap3* KO mouse model is very relevant to study compulsive behaviors. Therefore, to appraise the involvement of cognitive flexibility in compulsive behaviors, we propose to assess this dimension through a translational approach in both OCD patients and *Sapap3* KO mouse model in a similar way.

Indeed, most of assessment tools have been developed independently between species, leading to limited correspondence between human and animal tasks. The few studies assessing cognitive flexibility in animal models of compulsive behavior perfectly illustrate such an issue. Contrary to human tasks, they rely in most cases on spatial discrimination (15–17) which hinders the proper data transposition from animal models to humans and vice versa (18, 19). Thus, it is essential to develop these procedures in parallel to ensure the coherence of the task parameters and psychometric properties (20, 21). These cross-species developments are essential to provide insights that would be impossible to glean from research in a single specie (22), by using analogous methodologies in animals and humans within the same study (23, 24).

Studies exploring cognitive flexibility using reversal learning (25–28), task switching (29–31), and intra/extra-dimensional set shifting (32–34) paradigms, have yet failed to show consistent deficits in OCD (35). Beyond methodological reasons (e.g. small sample sizes), the clinical heterogeneity of OCD patients (36–41) may have contributed to these discrepant results (42–44). In animal models of compulsive behavior, despite the limited number of behavioral studies, the three that have used reversal learning paradigms, all reported cognitive flexibility deficits (15, 16, 45). But, as for humans, some innovative studies found evidence for inter-individual variability of cognitive traits in animal models (46), pointing out its necessary consideration in animal studies.

We therefore propose here a cross-species approach to study the involvement of cognitive flexibility in compulsive behaviors. To the best of our knowledge, this study is the first to address this question in parallel in human and mice. For this purpose, we have developed an innovative high throughput behavioral setup for mice that allow us to reliably test multiple times the performance of individual subjects in a non-spatial visual reversal learning task, as it is performed in human studies. Finally, we ensured the correct interpretation of our results by recruiting a sufficiently large sample in both species, thereby allowing consideration in our analyses of the intra-species phenotypic heterogeneity.

Methods and materials

Ethics

The protocol for human participants was approved by the Medical Ethical Review Committee of the Pitié-Salpêtrière Hospital (ID RCB n° 2012-A01460-43). Each subject gave its written informed consent prior to the study.

Each animal experiment was approved by the Ethic committee Darwin/N°05 (Ministère de l'Enseignement Supérieur et de la Recherche, France) and conducted in agreement with institutional guidelines, in compliance with national and European laws and policies (Project n° 00659.01).

Samples

Forty patients diagnosed with OCD according to the DSM-V criteria and a score greater than or equal to 16 in the Yale-Brown Obsessive-Compulsive Scale (YBOCS) were included in this study. Forty healthy comparison subjects were matched individually according to age, sex, handedness, school education as well as for IQ (estimated by the French National Adult Reading Test, fNART (47)). For each patient, the equivalent dose of fluoxetine were calculated (48). Fifty-two mice (26 Sapap3-null (KO) and 26 age matched wildtype (WT) littermates, male, 6-7 months old, C57BL/6J background) were used. The characteristics of the samples for both species are summarized in Table 1. See Supplementary Methods and Materials for more details.

Mouse automatized experimental chamber

The mice were placed 24h a day in an automatized experimental chamber (Figure 1A) which was designed to allow the most ecological possible assessment by avoiding any daily manipulation and methodological constrains (like food deprivation) that could affect animals normal behaviors (49–51). To control for any environmental influence, the mice underwent the task by pair, a KO and its WT littermate starting at the same time. Prior to the beginning of the task, the mice were acclimated to the experimental chamber and the food for 24 hours with a pellet delivered each time they nose poked in the pellet receptacle. After this acclimation phase, they underwent automatically two phases of instrumental pre-training before the beginning of the task (Supplementary Figure S1).

Reversal learning paradigm

The human version of the reversal learning task (Figure 1B left) was administered in a computerized version adapted from Valerius et al. (28) and coded in MatLab R2013b (MathWorks) and the Psychophysics Toolbox v3 module. As classically done in human behavioral studies (52), to make reversals less obvious, probabilistic errors were interspersed so that there was a 20% chance of receiving a misleading feedback. The

task ended after the completion of 20 reversals. The mouse version of the task (Figure 1B right) was the same as the human version, with the feedback being deterministic as the main difference (i.e. there were no probabilistic error). Particularly, just as in the human task, the rewarded side was contingent to the stimuli presented on the screens to exclude any simple spatially-guided or even cue-guided strategy. The task ended after completion of 5 reversals, representing around 2000 of trials performed in approximately 3 weeks (Figure 1A).

For both species, the main behavioral parameters to assess subjects' performance were the number of trials needed to reach the reversal criterion and the number of perseverative errors following a reversal (reversal errors). For mice, this latest parameter was estimated as a proportion of errors in the perseverative phase (53, 54) which was defined as a block of trials following a reversal above 60% error rate according to a change point analysis adapted from Gallistel et al. (55). The probability of a spontaneous strategy change (SSC, i.e. switching to the alternative, unrewarded stimulus despite positive feedback; also defined as response lability) and the number of perseverative errors following a SSC (SSC errors) were used as secondary parameters. The acquisition phase, defined as the trials needed to reach the reversal criterion for the first time, is thought to measure a baseline capacity for learning associations, and not a reversal learning deficit (56). It was therefore analyzed separately.

See the Supplementary Methods and Materials for a more detailed description of the tasks and the behavioral apparatus.

Statistical analysis

Following recommendations from the community (57, 58), we used Bayesian statistics to overcome the multiple shortcomings of NHST (59). See the Supplementary Methods and Materials for more details.

All the analyses were performed in JASP v0.9.2 (60). For group comparisons, two-tailed (or one-tailed when justified, indicated by $BF_{\pm 0}$) Jeffreys–Zellner–Siow (JZS) paired t-tests (61) were carried out to analyze differences in continuous variables with an uninformed Cauchy prior ($\mu = 0$, $\sigma = {}^{1}/_{\sqrt{2}}$), and two-tailed Gunel-Dickey (GD) contingency tables tests (62) for independent multinomial sampling were carried out to analyze differences in categorical variables with a default prior concentration of 1. For multiple-groups comparisons, we used JZS ANOVA (63) with an uninformed multivariate Cauchy prior ($\mu = 0$, $\sigma = {}^{1}/_{2}$) followed by post-hoc two/one-tailed JZS t-tests and two-tailed GD contingency tables tests for joint multinomial sampling. When appropriate, effect sizes are reported, i.e. Cohen's *d* with its 95% Credible Interval (95CI) for JZS t-tests and the η^2 for JZS ANOVA. For correlation analysis, two-tailed JZS Pearson correlation tests (64) were used with an uninformed stretched β prior (width 1). The correlation coefficient *r* is reported along with its 95CI. The categorical variables are expressed in percent and the continuous variables are expressed by their mean ± standard deviation. All values are rounded to two decimal places.

Cluster analysis

To search for a potential sub-group of WT or KO mice which would behave differently in our task, we performed a two-step cluster analysis (65) using the four behavioral parameters extracted from our task (number of trials to reversal, reversal errors, SSC probability and SSC errors). This algorithm has the advantage to rely on the Bayes Information Criterion to automatically choose the number of clusters to retain; avoiding any subjective and biased selection. This first analysis was followed by a stepwise discriminant analysis as a confirmatory procedure. These analyses were performed in SPSS v25 (IBM). See Supplementary Methods and Materials for more details.

Results

OCD patients and KO mice taken as a whole do not significantly differ from their controls

In a reversal paradigm, it is traditionally expected that an impairment will result in a higher number of trials needed to reach reversal criterion, underpinned by a higher number of reversal errors. Considering the number of trials needed to reach reversal criterion (Figure 1C), no group differences were found for both humans (BF_{10} = 0.64, *d* = 0.27 [0.04 0.77]) and mice (BF_{10} = 0.7, *d* = 0.33 [-0.1 0.92]). Similarly, no significant group differences were found considering the number of reversal errors (Figure 1C) for both humans (BF_{10} = 1.5, *d* = 0.35 [0.07 0.88]) and mice (BF_{10} = 0.44, *d* = 0.25 [-0.2 0.83]). The other behavioral parameters support this lack of difference between groups for both species (Table 2).

Only a subgroup of OCD patients and a subgroup of KO mice are impaired

In OCD patient, depression/anxiety levels, disease severity and antidepressant dose did not influence task performance (Table 3). To exclude a possible non-specific learning impairment might explain the behavioral deficit in the reversal phase we assess the correlation between the acquisition phase and the reversal phase: our results suggest this was not the case (Table 3). Thus, considering the fact that cognitive functions are likely to be differently affected across OCD subtypes (25), we verified if certain symptoms subtypes had an effect on the task performances (Table 3). It appeared that only checking symptoms severity increases the number of trials needed to reach the reversal criterion (Figure 3A). Regarding this observation, we conducted a subgroup analysis by separating the OCD patients with predominantly checking symptoms from the others. Twenty-one OCD "checkers" were separated from the original group. The three resulting new groups (OCD "checkers", OCD "non-checkers" and healthy subjects) were not different in terms of demographic characteristics (Table 1). Considering the clinical characteristics (Table 1), the two OCD groups were similar except for the checking and washing scores as expected but also for psychiatric comorbidities with a higher rate of comorbid anxiety disorder among OCD "checkers".

As for OCD patients, we tried to figure out if we could find the same heterogeneity in the KO mice. Previous studies in rodents tend to show an association between compulsive behaviors and perseverative responding in spatial reversal learning paradigms (15, 16, 45). Interestingly, when we first considered grooming level, we did not find any correlation with the main behavioral parameters (Table 3). Thus, we performed a two-step cluster analysis which identified two clusters within the KO mice but none in WT controls (Figure 3C; see Supplementary Results for more details). Fourteen KO mice constituted the "unimpaired" group and twelve the "impaired" group. The two KO subgroups were similar in terms of weight at the beginning of the task and grooming level (Table 1).

Considering the number of trials needed to reach the reversal criterion (Table 2), a group effect was found for both humans (BF_{10} = 3.98, η^2 = 0.11, Figure 2B) and mice (BF_{10} > 100, η^2 = 0.35, Figure 2D), with an absence of comorbid anxiety disorder effect in humans (Supplementary Table S1). Indeed, OCD "checkers"

needed more trials than both OCD "non-checkers" (BF_{+0} = 4.66, *d* = 0.74 [0.08 1.25]) and healthy controls (BF_{+0} = 9.32, *d* = 0.67 [0.14 1.17]); with no difference between the latter two groups (BF_{10} = 0.28, *d* = 0.01 [-0.5 0.5]). Similarly, "impaired" KO mice needed more trials than WT controls (BF_{10} > 100, *d* = 1.37 [0.54 2.17]); with no difference between "unimpaired" KO mice and WT controls (BF_{10} = 0.43, *d* = 0.29 [-0.35 0.82]).

This impairment is not explained by a greater perseveration but by a higher response lability

Considering that only checking symptoms were associated with an impairment in OCD patients, we wanted to see if it could be explained by a greater perseveration. We did not find a correlation between checking symptoms severity and the number of reversal errors (Table 3). This was confirmed by the subgroup analysis with an absence of a group effect on the number of reversal errors (BF_{10} = 0.72, η^2 = 0.06, Figure 3A). In mice, we found a group effect relative to the proportion of reversal errors (BF_{10} > 100, η^2 = 0.34, Figure 3A) as "impaired" KO mice made fewer reversal errors than WT controls (BF_{10} = 53.84, *d* = 1.51 [0.35 1.93]) and no difference between "unimpaired" KO mice and WT controls (BF_{10} = 0.71, *d* = -0.48 [-1.02 0.19]).

When we looked at secondary behavioral parameters, we found that checking symptoms induce a higher response lability in OCD patients with a positive correlation between checking symptoms severity and SSC probability while no correlation was found with the other parameters (Table 3). The subgroup analysis supported this result with differences between human groups found as we considered the SSC probability (BF_{10} = 1.19, η^2 = 0.08, Figure 4B); as for mice (BF_{10} > 100, η^2 = 0.41, Figure 4B). More precisely, OCD "checkers" were more labile than both healthy controls (BF_{+0} = 3.51, *d* = 0.53 [0.08 1.02]) and OCD "non-checkers" (BF_{+0} = 2.22, *d* = 0.59 [0.06 1.1]). Notably, these two latter groups did not differ from each other (BF_{10} = 0.29, *d* = 0.09 [-0.41 0.57]) and no comorbid anxiety disorder effect was found (Supplementary Table S2). The same results were obtained in mice with "Impaired" KO mice more labile than WT controls like OCD "checkers" (BF_{10} = 24.64, *d* = 1.22 [0.33 1.82]), and "unimpaired" KO mice less labile than WT controls (BF_{10} = 5.24, *d* = 0.91 [0.12 1.45]).

Regarding other behavioral parameters, we did not observe any group effect in humans but a group effect was found in mice on the mean number of SSC errors (BF_{10} > 100, η^2 = 0.31) with WT controls making more SSC errors than both "impaired" KO mice (BF_{10} > 100, *d* = 1.61 [0.62 2.24]) and "unimpaired" KO mice (BF_{10} = 2.63, *d* = 0.78 [0.02 1.3]) (Table 2).

Thus, for both species, a higher response lability increases the number of trials needed to reach the reversal criterion without increasing the number of reversal errors. In humans, this higher response lability is induced by checking symptoms. Importantly, both OCD "checkers" and "impaired" KO mice show response lability only in a reversal context and not during the acquisition phase (see Supplementary Results).

Discussion

Our results emphasize the importance of considering clinical subtypes with an absence of identified deficits in our reversal learning task when we consider OCD patients as a homogeneous group. However, our large sample size allowed us to reconsider them and identify a subgroup of impaired patients with checking symptoms in our task. Indeed, we showed that only the severity of checking symptoms correlated positively with the number of trials needed to reach the reversal criterion. Thus, we separated the checking patients from the others and showed that those only were impaired. This is in line with the results of a recent meta-analysis demonstrating that the cognitive profile of checking patients is more altered than other OCD patients (mainly washers) (66). The same observation was made in *Sapap3* KO mice, a well-described mouse model suffering of compulsive grooming behaviors, with no difference compared to WT mice when considered as a homogeneous group. Importantly, the compulsive behavior in the *Sapap3* KO mouse did not predict performance in cognitive flexibility in our reversal learning task. Thus, we conducted a two-step cluster analysis based on the task performance. Thanks to our large sample size, we identified a subgroup of KO, but not WT mice, with a similar deficit, as for OCD patients. These cross-species results are a powerful argument in favor of the heterogeneity of cognitive deficits in compulsive disorders and stresses the importance of considering this heterogeneity even in animal models. Highlighting such results was possible thanks to our translational approach based on the development of a cross-species task (see Supplementary Discussion for the rationale behind the choice of the reversal learning paradigm). Moreover, these results are strengthened by the recent study of Manning et al. (67) which, although using a spatial paradigm, found that about half of their *Sapap3* KO mice were unable to learn the reversed association without any difference in grooming level between the two subgroups. However, they also found a reduced level of locomotor activity in *Sapap3* KO mice with the impaired subgroup progressively disengaging from their task. Thus, their reversal deficit could be explained by a reduced exploration underpinned by this hypoactivity. This one could be a consequence of the higher anxiety level of the *Sapap3* KO mice (11) which would be exacerbated in their impaired subgroup by a greater sensitivity to the daily manipulations. Indeed, it has been shown to be stressful and thus to skew the behavioral outcomes (51). These possible biases are not present in our study thanks to our ecological design with an engagement level maintained across the task and even higher among the *Sapap3* KO mice compared to WT mice; with no significant difference between the two *Sapap3* KO subgroups (Supplementary Figure S2).

Just as important and surprising, we found that in both species, an impairment in our reversal learning task does not comes out in a greater perseveration in the previously correct response after reversal, contrary to what Manning et al. (67) found, but in a greater response lability in the reversal conditions (44, 68). This response lability might yet be seen as a form of perseveration: the subject may have more difficulty to get rid of the previous association that keeps influencing him long after the reversal. The fact that this deficit is expressed only in the reversal conditions supports this hypothesis. However, it could also be explained by alternative hypotheses since it has been shown that OCD patients have decision making (69) and information sampling (70) deficits specific to situations of uncertainty. Indeed, the reversal event drastically increases the level of uncertainty and consequently the higher response lability could only be the consequence of these deficits. This assumption makes

sense when considering the isolated subgroup of “checkers’ patients displaying a higher degree of doubt. Other studies suggest the presence of a visual processing impairment in OCD (71–73). Thus, the use of abstract visual stimuli that may share some similarities would exacerbate this impairment, making the deficit in our task totally independent of the reversal and strictly unrelated to cognitive flexibility. However, these studies suggest that this deficit affects all OCD patients and not only the “checkers”. Hence, we should have found a deficit in all our patients, which was not the case. Nevertheless, further research is needed with dedicated designs to address these points.

In light of these results, would the subgroup of impaired KO mice be an equivalent of our checking patients? It would be an over-interpretation to call this subgroup "checking" mice. But these mice not differing from other KO mice by grooming, what underlies their deficit? Although inbred strains are supposed to be characterized by the same genetic background across all mice, this one is not necessarily stable over time and may result in the emergence of new phenotypic traits due to a genetic drift. However, it has been shown that the C57BL/6J strain (our mice genetic background) is one of the least susceptible strains to this kind of phenomenon (74). Furthermore, we precluded this assumption by checking the genealogy of our mice with no identified genealogical specificity for the impaired KO mice subgroup (Supplementary Figure S3). Another hypothesis would be an inter-individual variability of epigenetic and/or environmental origin. It was notably shown that phenotypic variability can emerge from variation in epigenetic regulation and environmental factors despite a genetically homogeneous population and the attention paid to achieving an identical controlled environment across individuals (75–78). Examples include work in genetically homogeneous WT C57BL/6J mice (79) and healthy rats (80) showing variability from one individual to another in the expression of flexible behavior underpinned by variability in serotonin levels within the OFC. As we do not identify a subgroup in our WT mice based on the task performance, we could think that such variability might also exist in our mice without causing any impairment in our task. Thus, it would only be a risk factor whose sole interaction with the *Sapap3* KO mutation would lead to an impairment.

In conclusion, our findings demonstrate the benefits of a well-conducted translational approach that allowed us to obtain robust similar results within the two species. We confirm here that OCD is not a homogeneous disorder and therefore the necessity to consider the phenotypic heterogeneity in both patients and animal model to study their cognitive profile. Moreover, our results go against the current literature by showing that compulsive behavior is not necessarily associated with a deficit in a reversal learning task. Contrary to what one might expect, this study also demonstrates that a deficit in this kind of task can manifest itself not through a greater perseveration but through a greater response lability in a reversal situation as demonstrated in a subcategory of subjects exhibiting compulsive behaviors, both in humans (checking patients) and mice (subgroup of *Sapap3* KO mice).

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Tables

Humans						
	Healthy (H)	**OCD**	**BF_{10}**	**Checkers (C)**	**Non-checkers (NC)**	**BF_{10}**
Sample size	40	40		21	19	
Gender (M/F)	15/25	15/25	0.26	10/11	5/14	0.44
Hand (R/L)	35/5	34/6	0.2	16/5	18/1	0.34
Age in years	40.28 (13.59)	40.15 (13.22)	0.18	41.9 (12.78)	38.21 (13.77)	0.15*
Education in years	5.43 (2.19)	5.15 (2.69)	0.37	5.1 (3.24)	5.21 (1.99)	0.13*
fNART IQ	108.18 (6.76)	107.4 (6.87)	0.2	106.81 (7.12)	108.05 (6.71)	0.14*
BDI	0.8 (1.34)	12.53 (6.56)	>100	11.05 (5.09)	14.16 (7.68)	>100*: H < C = NC
BIS-10	45 (9.89)	47.03 (11.75)	0.23	48.57 (12.14)	45.32 (11.38)	0.21*
STAI-A	40.40 (4.38)	62.60 (13.07)	>100	62.81 (10.08)	62.37 (16.04)	>100*: H < C = NC
STAI-B	36.05 (5.97)	65.38 (9.05)	>100	64.76 (5.65)	66.05 (11.88)	>100*: H < C = NC
OCI-R:						
Total score	3.88 (4.23)	30.43 (8.86)	>100	31.19 (7.85)	29.58 (10)	>100*: H < C = NC
Order subscore	1.45 (1.88)	6.28 (3.06)	>100	6.14 (3.14)	6.42 (3.04)	>100*: H < C = NC
Washing subscore	0.53 (1.06)	6.45 (4.59)	>100	4.43 (4.23)	8.68 (3.96)	>100*: H < C < NC
Checking subscore	0.35 (0.89)	5.68 (3.87)	>100	8.52 (2.23)	2.53 (2.65)	>100*: H < NC < C
Hoarding subscore	1.1 (1.37)	3.85 (2.93)	>100	4.29 (2.26)	3.37 (3.53)	>100*: H < C = NC
Obsession subscore	0.38 (0.77)	5.53 (2.97)	>100	5.1 (2.41)	6 (3.5)	>100*: H < C = NC
Neutralization subscore	0.18 (0.5)	2.65 (2.86)	>100	2.71 (3.02)	2.58 (2.76)	>100*: H < C = NC
YBOCS		25.25 (5.29)		24 (4.84)	26.63 (5.54)	0.85
Taking an antidepressant:		28		16	12	0.74
with an AAP		4		2	2	0.24
with a benzodiazepine		7		4	3	0.3
Fluoxetine-equivalent in mg/d		53.73 (57.65)		46.74 (47.88)	61.45 (67.34)	0.4
Psychiatric comorbidities:						
Anxiety disorder		11		9	2	6.27
Eating disorder		1		0	1	
Age at onset		15.23 (5.88)		15.05 (5.64)	15.42 (6.28)	0.31
Duration in years		24.92 (13.95)		26.86 (15.45)	22.79 (12.14)	0.43
C57BL/6J Mice						
	WT (W)	***Sapap3* KO**	**BF_{10}**	**Impaired KO (I)**	**Unimpaired KO (U)**	**BF_{10}**
Sample size	26	26		12	14	
Age in days	200.12 (12.23)	199.35 (12.29)	0.25	199.67 (14.9)	199.07 (10.13)	0.16*
Weight in g	35.47 (4.99)	29.71 (2.88)	>100	29.13 (3.32)	30.21 (2.46)	>100*: W > I = U
Number of grooming bouts	5.38 (3.75)	12.12 (7.05)	>100	14.58 (8.55)	10 (4.82)	>100*: W < I = U
Time spent grooming in %	11.76 (19.18)	25 (20.43)	3.11	29.01 (24.2)	21.56 (16.72)	1.71*: W < I = U

Table 1. Demographic and clinical characteristics of the samples. *Mean (SD). A BF_{10} greater than one is in favour of a difference and vice versa. The further the BF_{10} is from one, the greater the evidence and vice versa. The * indicates a JZS ANOVA BF_{10} with the results of post hoc tests given after the BF_{10} value; "=" indicating an absence of difference. AAP: atypical antipsychotic.*

Humans						
	Healthy (H)	**OCD**	**BF_{10}**	**Checkers (C)**	**Non-checkers (NC)**	**BF_{10}^{ANOVA}**
Trials in acquisition phase	19.79 (7.29)	24.09 (9.89)	2.29	28.13 (11.59)	19.62 (4.74)	47.88: C > NC = H
Trials to reversal	26.09 (6.84)	29.09 (8.43)	0.64	31.87 (10.05)	26.02 (4.8)	3.98: C > NC = H
Reversal errors	1.64 (0.4)	1.48 (0.27)	1.5	1.46 (0.26)	1.51 (0.28)	0.72
SSC probability in %	4.1 (3.17)	5.2 (4.68)	0.41	6.47 (5.44)	3.8 (3.27)	1.19: C > NC = H
SSC errors	0.17 (0.19)	0.17 (0.16)	0.17	0.21 (0.17)	0.12 (0.15)	0.35
SCAPE probability in %	54.79 (22.53)	61.82 (15.26)	0.6	61.86 (14.78)	61.77 (16.17)	0.33
SCAPE errors	1.28 (0.16)	1.29 (0.21)	0.19	1.31 (0.25)	1.26 (0.15)	0.16
C57BL/6J Mice						
	WT (W)	***Sapap3* KO**	**BF_{10}**	**Impaired KO (I)**	**Unimpaired KO (U)**	**BF_{10}^{ANOVA}**
Trials in acquisition phase	464.66 (182.23)	438.39 (248.19)	0.22	560.08 (261.76)	334.07 (187.31)	2.35: U < I = W
Trials to reversal	437.7 (156.89)	554.39 (290.37)	0.7	746.87 (278.55)	389.4 (181.61)	>100: W = U < I
Reversal errors in %	25.84 (12.8)	22.08 (12.97)	0.44	11.1 (5.17)	31.49 (9.71)	>100: I < U = W
SSC probability in %	44.19 (3.65)	44.4 (4.09)	0.21	48.1 (1.88)	41.22 (2.36)	>100: U < W < I
SSC errors	0.57 (0.11)	0.45 (0.09)	27.74	0.41 (0.08)	0.48 (0.1)	>100: I < U < W

Table 2. Behavioral parameters. *Mean (SD). A BF_{10} greater than one is in favour of a difference and vice versa. The further the BF_{10} is from one, the greater the evidence and vice versa. For JZS ANOVA, the results of post hoc tests are given after the BF_{10} value with "=" indicating an absence of difference.*

OCD patients		
	Trials to reversal	**Reversal errors**
Trials in acquisition phase	BF_{10} = 0.28, r = 0.14 [-0.18 0.42]	
Fluoxetine-equivalent dose	BF_{10} = 0.24, r = -0.105 [-0.39 0.21]	BF_{10} = 0.31, r = 0.16 [-0.16 0.43]
YBOCS	BF_{10} = 0.2, r = 0.03 [-0.28 0.33]	BF_{10} = 0.2, r = 0.02 [-0.29 0.32]
BDI	BF_{10} = 0.34, r = -0.17 [-0.44 0.15]	BF_{10} = 0.21, r = 0.05 [-0.25 0.35]
STAI-A	BF_{10} = 0.22, r = 0.08 [-0.23 0.37]	BF_{10} = 0.21, r = 0.03 [-0.25 0.35]
STAI-B	BF_{10} = 0.22, r = -0.08 [-0.37 0.23]	BF_{10} = 0.2, r = 0 [-0.3 0.3]
OCI-R Total score	BF_{10} = 0.2, r = -0.02 [-0.31 0.29]	BF_{10} = 0.33, r = 0.17 [-0.15 0.44]
OCI-R Checking subscore	BF_{10} = 2.96, r = 0.37 [0.06 0.6]	BF_{10} = 0.2, r = 0 [-0.3 0.3]
OCI-R Washing subscore	BF_{10} = 0.47, r = -0.22 [-0.48 0.1]	BF_{10} = 0.23, r = 0.1 [-0.21 0.38]
OCI-R Order subscore	BF_{10} = 0.27, r = -0.13 [-0.41 0.18]	BF_{10} = 0.2, r = 0.04 [-0.27 0.33]
OCI-R Hoarding subscore	BF_{10} = 0.2, r = 0.04 [-0.27 0.33]	BF_{10} = 0.24, r = -0.11 [-0.39 0.2]
OCI-R Obsession subscore	BF_{10} = 0.2, r = 0.02 [-0.29 0.32]	BF_{10} = 0.53, r = 0.23 [-0.09 0.49]
OCI-R Neutralization subscore	BF_{10} = 0.25, r = -0.12 [-0.4 0.2]	BF_{10} = 0.42, r = 0.2 [-0.11 0.47]
	OCI-R Checking	
SSC probability in %	BF_{10} = 4.54, r = 0.4 [0.1 0.62]	
SSC errors	BF_{10} = 0.58, r = 0.24 [-0.08 0.5]	
SCAPE probability in %	BF_{10} = 0.38, r = -0.19 [-0.46 0.13]	
SCAPE errors	BF_{10} = 0.42, r = 0.2 [-0.11 0.47]	
***Sapap3* KO mice**		
	Trials to reversal	**Reversal errors in %**
Number of grooming bouts	BF_{10} = 0.32, r = 0.16 [-0.23 0.49]	BF_{10} = 0.65, r = -0.29 [-0.59 0.11]
Time spent grooming in %	BF_{10} = 0.29, r = -0.12 [-0.46 0.27]	BF_{10} = 0.49, r = -0.25 [-0.55 0.15]

Table 3. Correlation matrix. *A BF_{10} greater than one is in favour of a correlation and vice versa. The further the BF_{10} is from one, the greater the evidence and vice versa.*

Figures

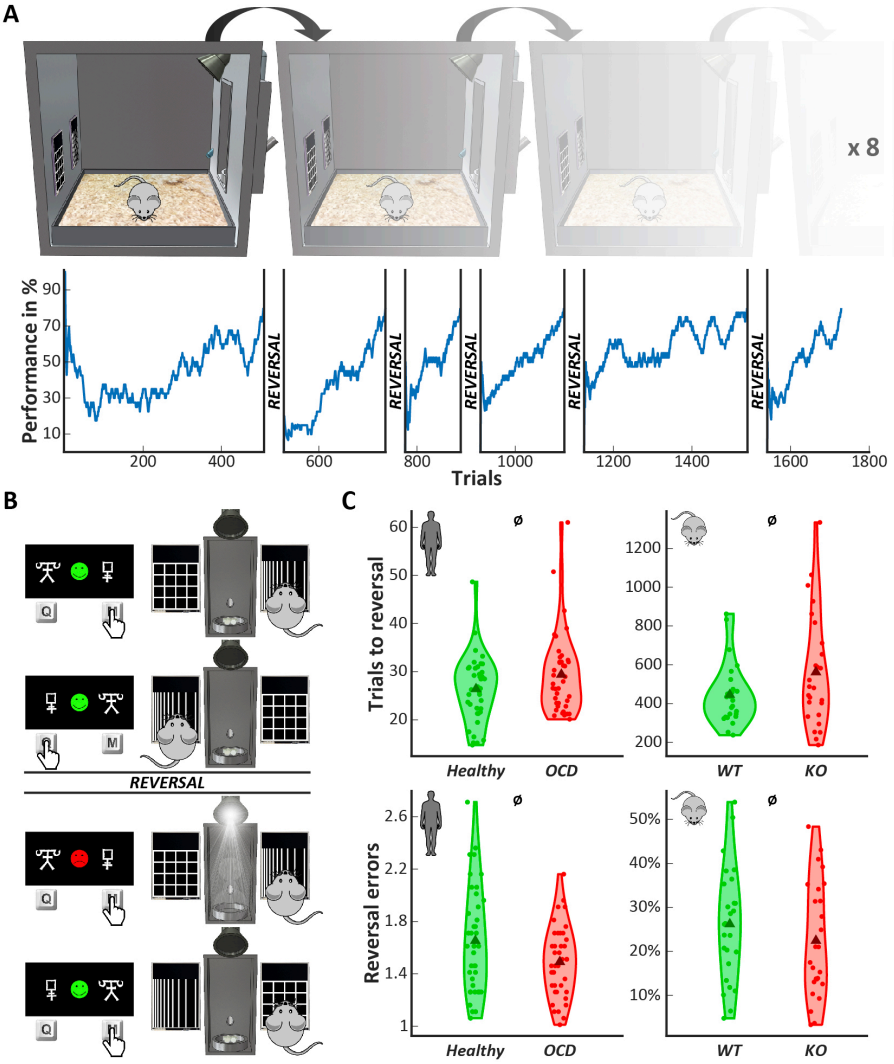

Figure 1. The reversal learning task. **(A) Up:** Illustration of the behavioral apparatus. 8 boxes are running in parallel with mice continuously living and working without any human intervention. *Left of a box: capacitive touchscreens. Frontward right of a box: pellet dispenser. Backward right of a box: water dispenser. Up right of a box: LED spot light.* **Down:** Performance of one mouse across the five reversals. The drop in performance after each reversal indicates that the mouse has properly learned the stimulus-reward association. *Blue line: performance on a 40-trial sliding window.* **(B)** Design of the human (left) and the mouse (right) versions of the reversal learning task. *On each trial, a pair of stimuli is displayed on the screens and the subject has to pick one. Depending on their choice (white hand/mouse) a positive (green smiley/pellet reward) or a negative (red smiley/aversive light) feedback is provided. By trial and error, the subject must find the positively-rewarded symbol. After the subject has repeatedly picked the correct symbol (see detailed criteria in Supplementary Methods and Material), reward contingencies are surreptitiously reversed and the previously positive stimulus become negative (and vice versa), yielding reversal errors on the first trials after the reversal before the subject adapt to the new contingencies.* **(C)** No difference was found between groups when taken as a whole for both humans (left – n = 40 per group) and mice (right – n = 26 per group), either when considering the number of trials needed to reach the reversal criterion (Up) or the number of reversal errors (Down). *Triangle: group mean. Dot: individual mean.* $^{\emptyset}$*:* $BF_{10} < 1$.

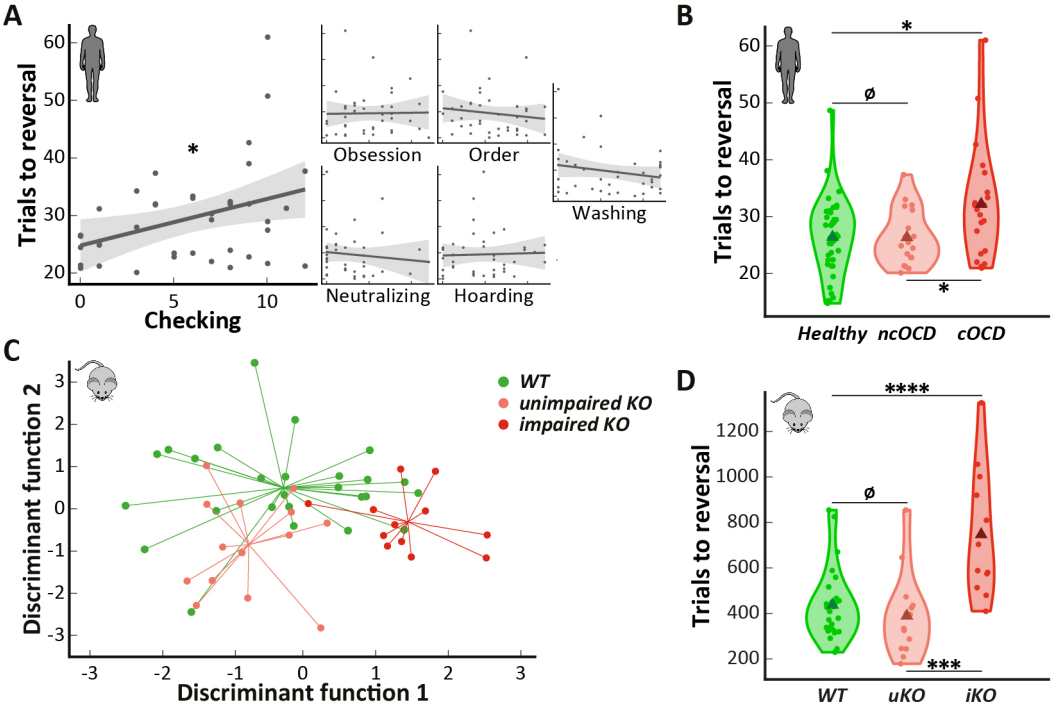

Figure 2. Only a subgroup of OCD patients and KO mice is impaired. **(A)** Only the severity of the checking symptoms measured by the OCI-R checking subscore predicts the number of trials needed to reach the reversal criterion. The higher the checking symptoms severity, the higher the number of trials needed. *Dark line: linear fit. Grey area: confidence interval.* **(B)** Based on this result, we segregated OCD patients with predominantly checking symptoms from the others and found that those ones only were impaired in terms of trials needed to reach the reversal criterion. *ncOCD: "non-checkers". cOCD: "checkers". Triangle: group mean. Dot: individual mean.* **(C)** A stepwise discriminant analysis was performed on the whole mice sample on the basis of the four behavioral parameters extracted from our task (number of trials to reversal, reversal errors, SSC probability and SSC errors) to confirm the two clusters identified within the KO mice by the two-step cluster analysis. The classification showed that overall 71.2% of mice were correctly labeled with 83.3% of the "impaired" KO mice correctly classified (16.7% were classified as WT controls) vs 50% for the "unimpaired" KO mice (50% classified as WT controls). *The lines intersection indicates the group's centroid.* **(D)** Only the "impaired" KO mice needed more trials to reach the reversal criterion compared to the other KO and WT mice. *uKO: "unimpaired" KO mice. iKO: "impaired" KO mice. Triangle: group mean. Dot: individual mean.*

*Ø: $BF_{10} < 1$. *: $BF_{10} \geq 3$. **: $BF_{10} \geq 10$. ***: $BF_{10} \geq 30$. ****: $BF_{10} \geq 100$.*

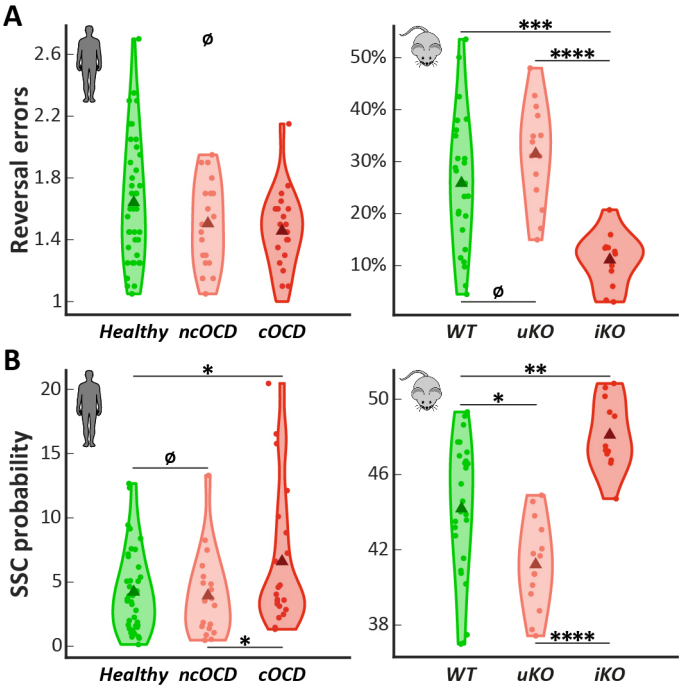

Figure 3. The impairment found in both OCD patients and KO mice subgroups is not explained by **(A)** a greater perseveration, with no difference between the human groups in term of reversal errors and with the "impaired" KO mice making fewer reversal errors than the other KO and WT mice. In fact, it turns out that **(B)** a higher response lability underlies this impairment with both OCD "checkers" and "impaired" KO mice showing an increased SSC probability compared to other groups. *ncOCD: "non-checkers". cOCD: "checkers". uKO: "unimpaired" KO mice. iKO: "impaired" KO mice. Triangle: group mean. Dot: individual mean.*

*ø: $BF_{10} < 1$. *: $BF_{10} \geq 3$. **: $BF_{10} \geq 10$. ***: $BF_{10} \geq 30$. ****: $BF_{10} \geq 100$.*