Full title: Mediodorsal thalamus is critical for updating during extra-dimensional shifts but not reversals in the attentional set-shifting task

Abbreviated title: Mediodorsal thalamus and choice response strategy updating

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Key words: updating, cognitive flexibility, learning, cognitive state, orbitofrontal cortex, anterior cingulate cortex, anterior thalamus, medial prefrontal cortex, prelimbic cortex, c-Fos

Abstract

Cognitive flexibility, attributed to frontal cortex, is vital for navigating the complexities of everyday life. The mediodorsal thalamus (MD), interconnected to frontal cortex, may influence cognitive flexibility. Here rats performed an attentional set-shifting task measuring intra-dimensional and extra-dimensional shifts in sensory discriminations. MD lesion rats needed more trials to learn the rewarded sensory dimension. However, once the choice response strategy was established, learning further two-choice discriminations in the same sensory dimension, and reversals of the reward contingencies in the same dimension, were unimpaired. Critically though, MD lesion rats were impaired during the extra-dimensional shift, when they must rapidly update the optimal choice response strategy. Behavioral analyses showed MD lesion rats had significantly reduced 'on-the-fly' correct second choice responses. Diminshed c-Fos expression in the prelimbic and orbitofrontal cortex was also documented. This evidence shows transfer of information via the MD is critical when monitoring and rapid updates in established choice response strategies are required.

Introduction

Cognitive flexibility describes our ability to quickly and selectively switch our thoughts, responses, or behavior to everyday dynamic situations. This capacity to rapidly update or alter one's actions conveys evolutionary benefit and is key to survival (Koechlin et al., 2003; Rougier et al., 2005). Cognitive flexibility shows marked changes or declines in neurodegenerative disorders, like Parkinson's disease, and in neurodevelopmental diseases, like schizophrenia (Andrews et al., 2006; Barch et al., 2009; Giraldo-Chica et al., 2018).

Cognitive flexibility is not unique to primates. Studies investigating the neural underpinnings of cognitive flexibility show that rats also can readily switch between attentional sets to optimise reward outcome (Birrell and Brown, 2000; McAlonan and Brown, 2003; Newman and McGaughy, 2011). Typically, these studies have focussed on various frontal cortex subregions. Yet, it is becoming increasingly clear that the cortex does not function in isolation, but rather, relies heavily on subcortical and peripheral inputs supplied by the thalamus (Sherman and Guillery, 2002; Guillery and Sherman, 2011; Halassa and Kastner, 2017). Clearly, the mediodorsal thalamus (MD) has a critical role in functions of frontal cortex during higher order cognitive processes across mammalian species (Alcaraz et al., 2018; Browning et al., 2015; Chakraborty et al., 2016, 2019; DeNicola et al., 2020; Ferguson and Gao, 2018; Miller et al., 2017; Mitchell et al., 2007a; Mitchell et al., 2007b; Pergola et al., 2018; Parnaudeau et al., 2013; Schmitt et al., 2017). Monkeys with MD lesions were found to have deficits when required to rapidly update 'on-the-fly' task-relevant information during complex visuospatial associative tasks (Browning et al., 2015; Chakraborty et al., 2016; Mitchell et al., 2007a) but not during recognition of the visuospatial associations (Mitchell and Gaffan, 2008). Thus the integrity of MD is particularly important for rapid reward-guided learning and implementing consistent choice strategies (Chakraborty et al., 2016). In monkeys and humans, the MD is densely interconnected with frontal cortex

77 areas involved in various aspects of cognitive flexibility, namely the dorsolateral and
78 dorsomedial prefrontal cortex (PFC), equivalent to the medial PFC (prelimbic (PrL) and
79 infralimbic) in rodents, the orbitofrontal cortex (OFC), ventrolateral PFC, and the dorsal
80 anterior cingulate cortex (Dajani and Uddin, 2015; Preuss, 1995). Recent neuroanatomical
81 work in rodents has shown the arrangement of MD projections to the frontal cortex allow for
82 the simultaneous sharing of information across multiple PFC cortical regions (Alcaraz et al.,
83 2016; Kuramoto et al., 2017). This distributed pattern of prefrontal innervation by the MD
84 appears to be especially true for the central (MDc) and medial (MDm) subdivisions, which
85 have mixed projections to OFC, medial PFC, and frontal association areas (Alcaraz et al.,
86 2016; Groenwegen, 1988). Although phylogenetic differences exist in the organisation of
87 rodent and primate frontal cortex, similar functional contributions to aspects of cognitive
88 flexibility are observed in monkeys and rodents after perturbations to similar areas of
89 agranular frontal cortex (Birrell and Brown, 2000; Bissonette et al., 2008; Dias et al., 1996;
90 Dias et al., 1997; McAlonan and Brown, 2003). Given there are similarities in
91 neuroanatomical connectivity between agranular frontal cortex and MD in rodents and
92 primates, it seems that cognitive flexibility and rapid updating deficits observed in monkeys
93 with MD lesions may also extend to rodents.
94 Thus, in the current study, rats with excitotoxic lesions to the MD or MD Sham
95 controls were run on a well-established test of cognitive flexibility – the intra-dimensional
96 (ID)/ extra-dimensional (ED) attentional set-shifting task (Birrell and Brown, 2000; Tait et
97 al., 2014; Tait et al., 2018) to test this premise and investigate any deficits in choice
98 responding. We used the standard 7-stage version comprising of multiple subtasks all
99 conducted within a single testing session (Birrell and Brown, 2000; Chase et al., 2012). In
100 rats, the ID/ED task has produced dissociable deficits after permanent cortical or thalamic

101 lesions, or neuropharmacological manipulations (e.g., Linley et al., 2016; McGaughy et al.,
102 2008; Tait et al., 2014; Tait et al., 2018; Wright et al., 2015).
103 In the current experiments, we predicted rats with MD lesions would show deficits
104 during the initial sensory acquisition (simple discrimination, SD) and the ED shift. Both the
105 SD and ED subtasks present online task changes that require rapidly altering response
106 strategies. Therefore, impaired SD and ED performance would be consistent with the
107 selective deficits in learning observed in other MD lesion rats (Hunt and Aggleton, 1998;
108 Mitchell and Dalrymple-Alford, 2005), or in primates with damage to the magnocellular
109 mediodorsal thalamic nucleus (MDmc: Browning et al., 2015; Chakraborty et al., 2016;
110 Chakraborty et al., 2019; Mitchell, 2015; Mitchell et al., 2007a). We also predicted our MD
111 lesion rats may show deficits during reversal subtasks given the reciprocal direct connectivity
112 with the OFC (Groenwegen, 1988; Krettek and Price, 1977; Ray and Price, 1992).
113 In addition to our behavioral analyses, we examined c-Fos immunoreactivity in the
114 interconnected OFC and PrL cortex after rats re-performed either the SD or ED subtasks to
115 establish the extent of changes in cortical neural activation after the MD lesion.
116
117 **2.0 Results**
118 **2.1 MD lesion site**
119 Of the 25 adult rats involved in this experiment, 15 sustained MD lesions and 10 were MD
120 Sham controls (see Materials and Methods for details). All 15 MD lesion rats had extensive
121 excitotoxic (NMDA) lesion damage (see **Fig. 1**) within the medial and central subdivisions of
122 the MD, as intended. In all cases the lesion affected between 80–90% of the central and
123 medial MD, sparing only the lateral portions. The MD was consistently shrunken, and at the
124 lesion site there was significant cell loss. In all cases, the adjacent anterior thalamic nuclei

(ATN) were spared. In two cases, there was unilateral (right-sided) damage in the lateral habenulae (LHb) and some damage to the central medial nucleus lying underneath the MD.

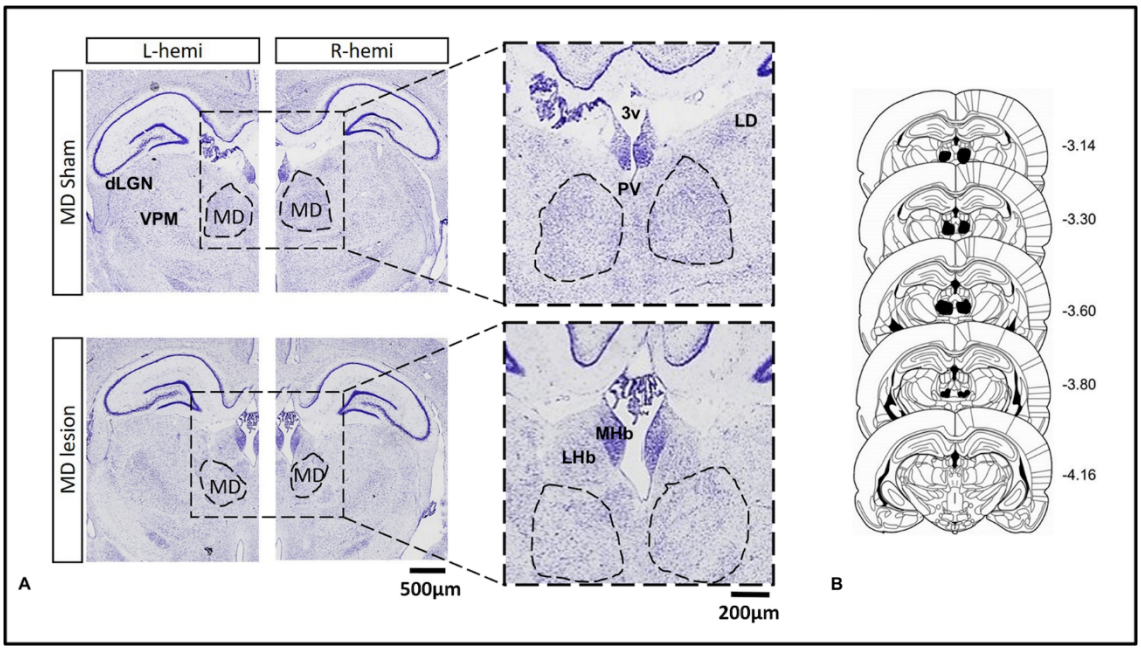

Figure 1. A. Photomicrographs of the thalamus in a MD Sham control rat (top) and a MD lesion rat (bottom). **B.** A series of coronal schematics throughout the mediodorsal thalamus showing the area of cell loss in the MD lesion group. Numbers refer to the distance from bregma (Paxinos and Watson, 2008). Abbreviations: 3v: third ventricle; dLGN: dorsal lateral geniculate nucleus; LHb: lateral habenula; LD: laterodorsal thalamus; MD: mediodorsal thalamus; MHb: medial habenula; PV: paraventricular nucleus; VPM: ventral posterior medial thalamus.

2.2 The MD and attentional set-shifting

Preoperatively, rats were pseudo-randomly assigned to either of two groups: MD lesion or MD Sham control, based on the number of trials needed to reach the learning criterion (six correct consecutive trials in nine trials) during the simple discrimination (SD) subtask. Preoperative data from one MD Sham control rat had to be discarded. An independent samples t-test confirmed there was no significant difference between the two groups during preoperative learning of the SD, $t(22) = 0.095$, $p > 0.05$, with rats from both groups requiring

144 a similar number of trials to reach criterion, MD lesion (Mean = 9.67, S.D. = 2.44) and MD
145 Sham control (Mean = 9.78, S.D.= 3.31).

146 Postoperatively, a repeated measures ANOVA with Stage (7 subtasks: SD, CD, REV1
147 ID, REV2, ED, REV3) as the within-group factor and Lesion_type (MD lesion vs MD Sham
148 control) as the between-group factor revealed a significant interaction, Stage × Lesion_type,
149 $F(6,138) = 63.65$, $p < 0.001$, a significant main effect of Stage, $F(6,138) = 184.73$, $p < 0.001$,
150 and a significant main effect of Lesion_type, $F(1,23) = 20.22$, $p < 0.001$ (see **Fig. 2A**). To
151 explore the interaction effect, *posthoc* comparisons of the simple main effects of Stage
152 (corrected for multiple comparisons, $p < 0.007$; alpha = 0.05 divided by 7 tests) were
153 computed. For the SD subtask, MD lesion rats required more trials to criterion (M = 16.67,
154 S.D. = 1.23) compared with MD Sham controls (M = 9.50; S.D. = 2.07), indicating that the
155 rats with the MD lesion were slower to acquire the new sensory discrimination. An
156 independent samples t-test confirmed this difference was significant, $t(23) = 10.88$, $p < 0.001$.
157 However, once the rats with MD lesion acquired the rewarded sensory dimension (to respond
158 either to the digging media, or to the odor), they were unimpaired in subsequent subtasks that
159 maintained the same rewarded sensory dimension, namely concurrent discrimination (CD):
160 $t(23) = 0.00$, $p = 1.0$, and intra-dimensional shift (ID): $t(23) = 1.08$, $p < 0.291$. MD lesion rats
161 were also not impaired in the reversals (REV1 and REV2) of the reward contingencies
162 associated with the learned exemplars completed after the CD subtask, REV1: $t(23) = 2.31$, p
163 < 0.030, or after the ID subtask, REV2: $t(23) = 1.34$, $p < 0.192$, although, all rats were
164 familiar with the reversal rule as they had completed the ID/ED task preoperatively (see
165 Materials and Methods). **Supplementary Figure 1** shows the mean and 1st and 3rd quartile
166 box plots with the smallest and largest numbers of postoperative trials to criterion (whiskers)
167 for the individual rats during each of the subtasks.

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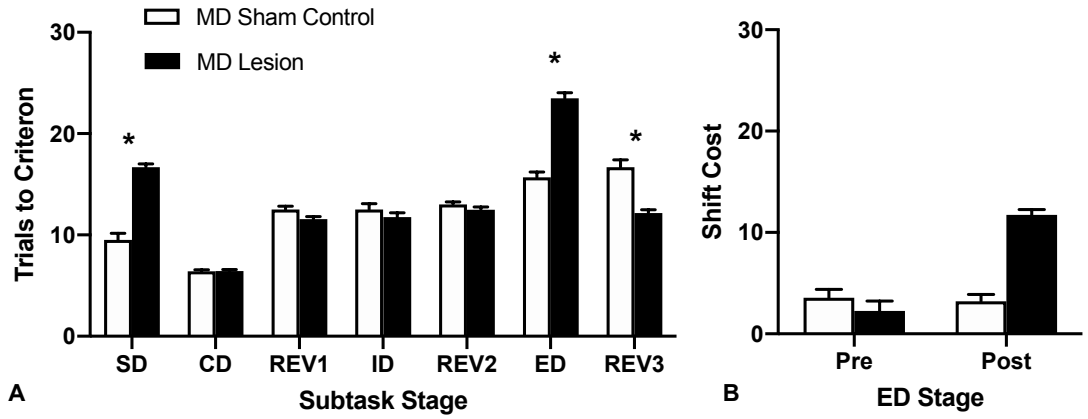

Figure 2. (A) Mean (+SEM) trials to criterion data for the attentional set-shifting task. MD lesion rats were significantly slower to learn the SD and the ED subtasks compared to MD Sham controls (**p* <0.001). MD Sham control rats also needed more trials to learn the ED, as expected. The MD lesion rats required significantly fewer trials to criterion to learn REV3, the reversal occurring immediately after the ED, compared to the MD Sham controls (**p* <0.001). **(B)** Mean (+SEM) trials to criterion shift cost data for the ED stage for preoperative (Pre) and postoperative (Post) testing sessions. The shift cost is computed as the number of trials to criterion in the ED minus the number of trials to criterion in the ID. Both groups of rats showed a shift cost during the ED, when they had to attend to the previously irrelevant dimension. The shift cost for the MD lesion rats in the postoperative test session was significantly different to the MD Sham controls.

For the extra-dimensional (ED) subtask, the rats had to shift their attention to the previously irrelevant sensory dimension. Thus, given the rats had acquired the attentional set strategy, as expected, all rats required more trials to criterion to learn the ED subtask. MD Sham controls required (M = 15.70; S.D. = 1.64) more trials to learn the ED when compared to trials required to learn the ID (M = 12.5; S.D. = 1.84). Similarly, the MD lesion rats required more trials (M= 23.47, S.D. = 2.07) compared with trials to learn the ID (M = 11.73; S.D. = 1.67; see **Fig. 2A**). A repeated measures ANOVA computing the trials to criterion for these two subtasks (ID vs ED) showed a significant Stage x Lesion_type interaction, $F(1,23) = 99.96$, $p < 0.001$, a significant effect of Stage, $F(1,23) = 306.11$, $p < 0.001$, and a significant effect of Lesion_type, $F(1,23) = 32.83$, $p < 0.001$ (see **Fig. 2A**). The interaction occurred as the MD lesion rats required significantly more trials to criterion to consistently implement a

192 new choice strategy in order to learn which of two stimuli was rewarded from the previously
193 ignored sensory dimension compared to the MD Sham controls, $t(23) = 10.00$, $p < 0.001$.

194 The additional repeated measures ANOVA of Session (Preoperative vs Postoperative)
195 shift cost (see **Fig. 2B**) between Lesion_type computed as the number of trials to criterion for
196 the ED subtask minus the number of trials to criterion for the ID subtask for each session
197 showed a significant Session x Lesion_type interaction, $F(1,22) = 44.06$, $p < 0.001$, a
198 significant effect of Sesion, $F(1,22) = 38.27$, $p < 0.001$, and a significant effect of
199 Lesion_type, $F(1,22) = 15.46$, $p = 0.001$ (see **Fig. 2B**). The significant interaction occurred as
200 there was a small shift cost for both groups during the preoperative test session. However,
201 during the postoperative test session only the MD lesion rats showed a significant shift cost
202 as a consequence of the task demands changing that required an adjustment to the previously
203 well-established response strategy ($p < 0.001$). By contrast, the MD Sham controls showed a
204 similar shift cost to their preoperative performance.

205 Interestingly, for REV3, the reversal subtask that occurred after the ED shift, MD
206 lesion rats required fewer trials to criterion (M = 12.13, S.D. = 1.25) compared with the MD
207 Sham controls (M = 16.7; S.D. = 2.26; see **Fig. 2A**). An independent samples t-test
208 confirmed this difference was significant, $t(23) = 6.51$, $p < 0.001$, suggesting a facilitation in
209 performance as a consequence of over-training experienced during the ED subtask.

210 **2.3 'On the fly' choice responses as a measure of rapid adaptability after MD lesion**

211 Given the observed deficits in the MD lesion group, we investigated the behavioral responses
212 made in the MD lesion or MD Sham control rats. Given the task design and a criterion of six
213 consecutive correct responses before switching to the next stage, overall during testing the
214 rats do not complete many trials. Nevertheless, we could determined whether the rats rapidly
215 adapted their choice responses in the here and now ('on the fly' choice responses) as

measured by the number of correct 2nd choice responses made, i.e. when the rat dug from the correct bowl only after visiting the incorrect bowl first but without digging in it, divided by the total number of correct responses (correct 1st and 2nd choice responses combined) for each session. During each subtask of the session, we recorded if the rat made a correct choice, either on the first attempt ('1st choice response'), or on the 2nd attempt ('2nd choice response'). We did not include error trials in this analysis.

A repeated measures ANOVA of total percent correct 2nd choice responses was conducted with Session (Preoperative vs Postoperative) as the repeated measure × Lesion_type revealed a significant interaction of Sesssion × Lesion_type, $F(1,21) = 9.40$, $p = 0.006$, a significant main effect of Session, $F(1,21) = 57.06$, $p < 0.001$, and a significant main effect of Lesion_type, $F(1,21) = 7.18$, $p = 0.014$ (see **Fig. 3A**). To investigate the interaction effect, *posthoc* comparisons of the simple main effects showed that the MD lesion rats (M = 28.18, SD = 7.61) made fewer correct 2nd choice responses compared to the MD Sham controls (M = 35.23, SD = 8.46). This deficit suggests the MD lesion rats had a diminished ability to fluidly bind together 'on-the-fly' their previous choice about what stimuli are worth sampling in order to rapidly update their choice response strategy, rather than a deficit in perseverative responding, or an inability to respond to negative feedback.

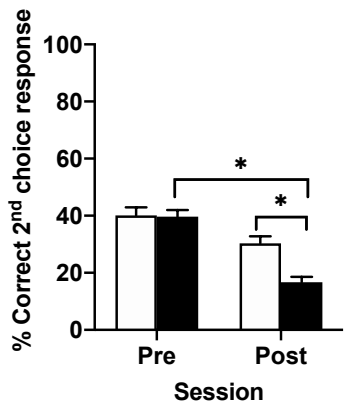

Figure 3. (**A**) Mean (+SEM) percent correct 2nd choice responses made during the preoperative and postoperative performance sessions of the attentional set-shifting task. MD lesion rats made fewer correct 2nd choice responses than MD Sham controls (* *p*'s = 0.001).

237 **2.4 Reaction time changes**

238 Reaction times (in seconds) for errors were also computed for each rat in separate
239 (preoperative (see **Fig. 4A**) and postoperative (see **Fig. 4B**)) analyses. Preoperatively, a
240 repeated measures ANOVA with Stage (7 subtasks: SD, CD, REV1 ID, REV2, ED, REV3)
241 as the within-group factor and Lesion-type (MD lesion vs MD Sham control) as the between-
242 group factor revealed a significant main effect of Stage, $F(1,21) = 23.99$, $p < 0.001$, but no
243 effect of lesion, and no interaction, F's <1.0. This result indicates there was no difference in
244 response times between the pseudo-randomly assigned groups (MD lesion and MD Sham
245 controls) preoperatively and that all rats responded quicker on errors trials as they moved
246 through subsequent subtasks within the session.

247 However, a separate repeated measures ANOVA of reaction times during
248 postoperative error trials revealed a significant interaction of Stage × Lesion_type, $F(6,132) =$
249 26.81, $p < 0.001$, a significant main effect of Stage, $F(6,132) = 22.45$, $p < 0.001$, and a
250 significant main effect of Lesion-type, $F(1,22) = 57.15$, $p < 0.001$ (see **Fig. 4B**). To
251 investigate the interaction effect, *posthoc* comparisons of the simple main effects (corrected
252 for multiple comparisons) were computed. Postoperatively, MD lesion rats responded slower
253 on error trials during the SD subtask, $t(22) = 10.09$, $p < 0.001$, the CD subtask, $t(22) = 7.65$, p
254 < 0.001, and the REV1 subtask, $t(22) = 4.44$, $p < 0.001$. However, for the final reversal
255 subtask, REV3, completed after the ED shift, MD lesion rats were quicker on the error trials
256 than MD Sham controls, $t(22) = 3.53$, $p = 0.002$. This result in combination with the reduced
257 trials to criterion required to complete this subtask (see **Fig. 2A**) suggests that the MD lesion
258 rats may have experienced overtraining due to the number of additional trials to criterion
259 required to adapt their choice responding in the ED subtask (Dhawan et al., 2019).

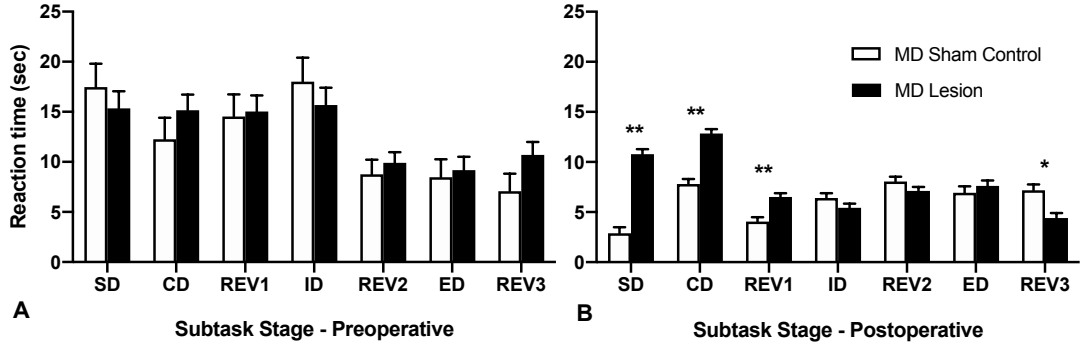

Figure 4. (**A**) Mean (+SEM) reaction time (secs) for preoperative error trials for MD Sham controls and MD lesion rats during each subtask of the ID/ED attentional set shifting task. (**B**) Mean (+SEM) reaction time (secs) for postoperative error trials for MD Sham controls and MD lesion rats during each subtask of the ID/ED attentional set shifting task (** $p < 0.001$; * $p = 0.002$).

2.5 Prefrontal cortex c-Fos immunolabeling

2.5.1 c-Fos expression after completing the simple discrimination (SD) subtask

Ten rats (five with MD lesion and five with MD Sham control) re-ran the SD subtask and were then placed into a dark holding cage for 90 mins prior to being perfused to detect changes in c-Fos expression levels in orbitofrontal (OFC) and prelimbic (PrL) cortex of the PFC. For these analyses, we used the raw cell counts (see Materials and Methods for further details). A 2 × 2 repeated measures ANOVA with PFC subregion (OFC, PrL) as the within-subject factor and Lesion_type (MD lesion vs MD Sham control) as the between-group factor showed no significant interaction, $F(1,8) = 3.33$, $p = 0.105$, although there was a significant main effect of subregion, $F(1,8) = 674.87$, $p < 0.001$, and a significant main effect of Lesion_type, $F(1,8) = 313.98$, $p < 0.001$ (see **Fig. 5A**). The MD lesion rats had reduced raw cell counts of c-Fos expression in both the OFC (M = 961.60, S.D. = 29.61) and PrL (M = 2316.80, S.D. = 144.51) compared to cell counts for the MD Sham controls (OFC: M = 1875.20, S.D. = 179.65; PrL: M = 3435.20, S.D. = 101.60; see **Fig. 5A and 6**).

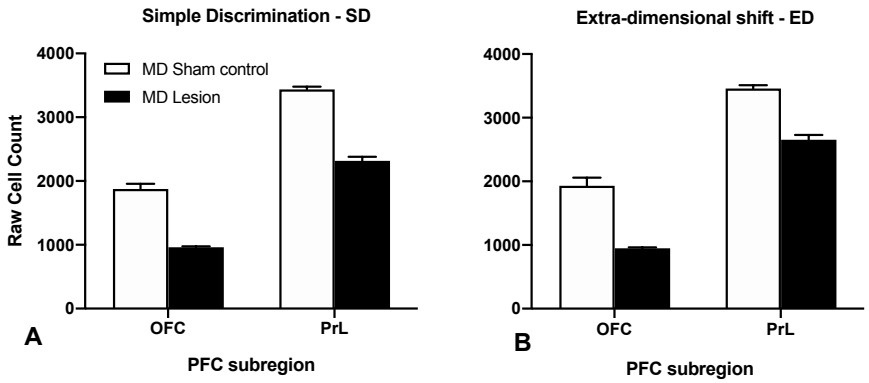

Figure 5. **(A)** Mean (+SEM) raw cell counts in two prefrontal cortex (PFC) subregions: orbitofrontal cortex (OFC) and prelimbic cortex (PrL) of c-Fos (immediate early gene marker of neural activity) expression in neurons in MD Sham controls and MD lesion rats, 90 mins after learning the simple discrimination (SD). **(B)** Mean (+SEM) raw cell counts of c-Fos expressing neurons in MD Sham controls and MD lesion rats, 90 mins after learning the extra-dimensional shift (ED).

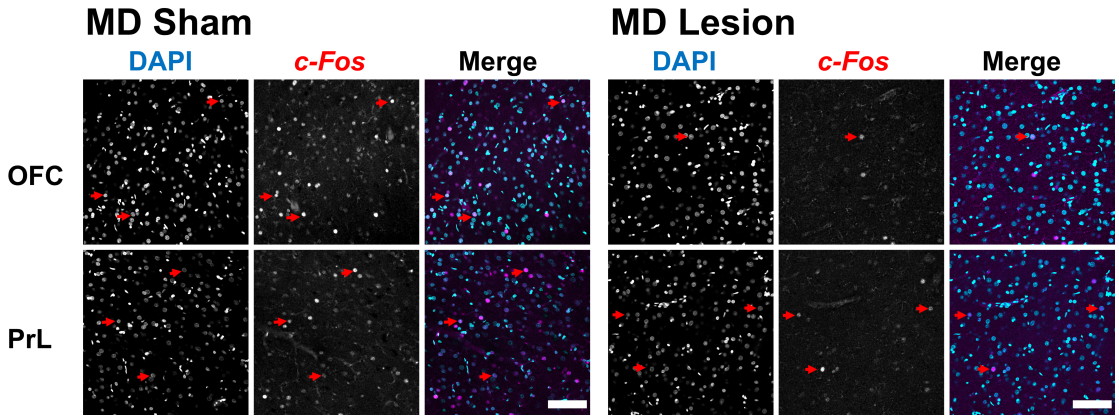

Figure 6. Example photomicrographs from a representative MD Sham control (left three panels) and a MD Lesion rat (right three panels) demonstrating the between group differences in c-Fos expression in two regions of the prefrontal cortex after completing the simple discrimination (SD) subtask. Images taken from the orbitofrontal cortex (OFC) are shown in the top row and images from the prelimbic cortex (PrL) are shown in the bottom row. DAPI was used to visualise the location of cell nuclei. Red arrows indicate locations of some of the c-Fos immunoreactive cells. The merged images combine both DAPI and c-Fos images together. See Materials and Methods for further details. Scale bar is 100 µm.

2.5.2 c-Fos expression after completing the extra-dimensional (ED) subtask

Ten rats (five with MD lesion and five with MD Sham control) were re-ran in 6 subtasks: SD, CD, REV1, ID, REV2, and ED, and were then placed into a dark holding cage for 90 mins

prior to being perfused to detect changes in c-Fos expression levels in the OFC and PrL subregions after the ED subtask. We cannot attribute the changes in c-Fos expression to performance in the ED subtask alone as all subtasks were completed in the 90 mins prior to perfusion. Raw cell counts were also computed for this analysis (see Materials and Methods for further details). A 2 × 2 repeated measures ANOVA showed that there was no significant interaction of subregion x Lesion_type, $F(1,8) = 1.09$, $p = 0.327$, but there was a significant main effect of subregion, $F(1,8) = 361.45$, $p < 0.001$, and a significant main effect of Lesion_type, $F(1,8) = 151.47$, $p < 0.001$ (see **Fig. 5B**). After completing the ED subtask, the rats with MD lesions had reduced c-Fos expression in the OFC (M = 947.20, S.D. = 37.35) and PrL (M = 2654.40, S.D. = 167.66) compared to MD Sham controls (OFC: M = 1929.60, S.D. = 286.91; PrL: M = 3459.20, S.D. = 115.60; see **Fig. 7**).

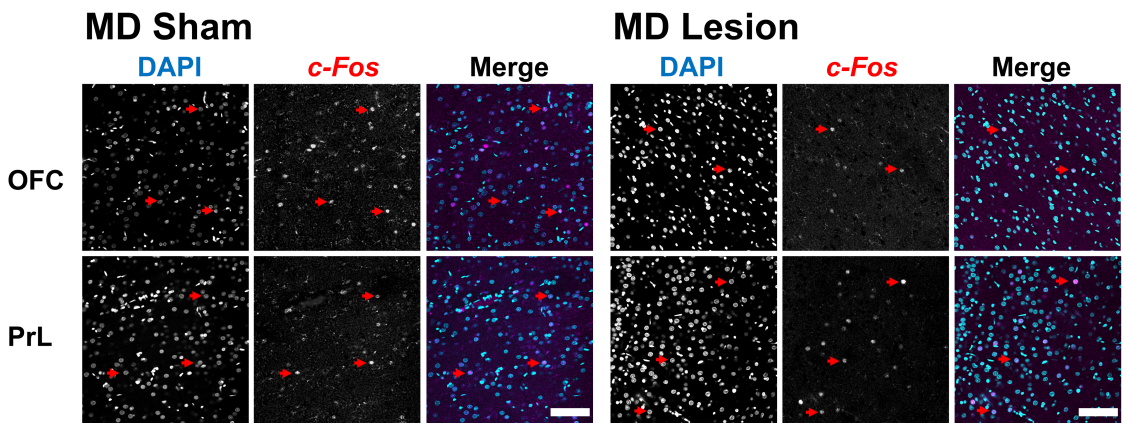

Figure 7. Example photomicrographs from a representative MD Sham control (left three panels) and a MD Lesion rat (right three panels) demonstrating the between group differences in c-Fos expression in two regions of the prefrontal cortex after completing the extra-dimensional discrimination (ED) subtask. Images taken from the orbitofrontal cortex (OFC) are shown in the top row and images from the prelimbic cortex (PrL) are shown in the bottom row. DAPI was used to visualise the location of cells. Red arrows indicate the locations of some c-Fos immunoreactive cells. The merged images combine both DAPI and c-Fos images together. See Materials and Methods for further details. Scale bar is 100 µm.

328 **3.0 Discussion**

329 This set of experiments investigated the active influence of rat mediodorsal thalamus (MD) in
330 cognitive flexibility. More specifically, we examined whether rats with excitotoxic lesions of
331 the central and medial MD were impaired in performing an attentional set-shifting task that
332 measures intra-dimensional (ID) and extra-dimensional (ED) shifts in attention to sensory
333 discriminations (digging media or odors). Our new results indicate that rats with MD lesion
334 required more trials to criterion to learn the optimal response strategy during the initial
335 simple discrimination (SD). Once this stable response strategy is learnt though, MD lesion
336 rats were able to attain an attentional set strategy as they acquired further two-choice
337 discriminations involving the same sensory dimension during the CD and ID shifts, and
338 during reversals (REV1 and REV2) of the reward contingencies associated to the exemplars.
339 However, when the relevant sensory dimension was switched, during the ED subtask, the
340 MD lesion rats were markedly impaired and required many more trials to update their choices
341 using a new response strategy, as measured by the significant ED shift cost. Further, for
342 REV3, the third reversal performed after the ED shift, the MD lesion rats showed facilitated
343 learning, suggesting they had received 'overtraining' as a consequence of completing many
344 more trials to reach criterion in the ED subtask. The analyses of behavioral responses
345 indicated that the MD lesion rats made significantly fewer correct 2nd choice responses
346 suggesting that information transfer via the MD is critical for the monitoring and updating of
347 choice response rules. Interestingly, similar updating deficits in choice responding have been
348 previously reported in rhesus macaques with magnocellular MD excitotoxic lesions
349 (Chakraborty et al*.,* 2016). Finally, decreased c-Fos expression (an immediate early gene
350 marker of neuronal activity) was observed in the OFC and in PrL after re-running the rats in
351 the SD and ED subtasks, providing imaging evidence for the widespread influence of the MD
352 on cortical areas.

353 These behavioral data accord somewhat with previous studies conducted in several
354 species that targeted equivalent frontal regions. For example, marmosets with lateral PFC
355 lesions (Dias et al., 1996) or rats with medial PFC lesions (Birrell and Brown, 2000) are also
356 impaired at the ED subtask, showing a similar ED shift cost as our MD lesion rats.
357 Conversely though, lesions to these comparative PFC regions in marmosets and rats did not
358 cause more trials to criterion during acquisition of the initial choice response strategy in the
359 SD subtask, indicating frontal regions contribute to different aspects of cognitive flexibility.
360 In contrast, while rats with anterior thalamic nuclei (ATN) lesions are not impaired in the ED
361 shift, they are impaired at acquiring the SD subtask (Wright et al., 2015). However, in
362 contrast to our MD lesion rats, rats with ATN lesions continued to be impaired during the CD
363 subtask and subsequent ID shifts (Wright et al., 2015) suggesting an intact ATN (a brain
364 structure adjacent to the MD but with markedly different cortico-thalamo-cortical
365 connectivity) is important in supporting the formation of an attentional set strategy.
366 Conversely, with more trials, our rats with MD lesions were able to acquire the
367 optimal choice response strategy during the SD subtask and apply this optimal rule during
368 subsequent subtasks, but they were markedly impaired at rapidly adapting these now well-
369 established choice responses when they had to now attend to the previously irrelevant sensory
370 dimension during the ED shift. The demands on cognitive flexibility, response inhibition, and
371 adapting behavioral responses after negative feedback are increased when the animals must
372 make an ED shift, assuming they have acquired the ID attentional set strategy in the first
373 place (Dhwana et al., 2019). The increased effort involved in adapting to these changes in
374 attention is measured by a shift cost, and it is expected that more trials to criterion are
375 required during learning the ED than during learning the ID shift. While the ID/ED shift cost
376 was higher for both groups (Fig. 2B), it was significantly increased for the MD lesion rats
377 compared to the MD Sham controls. As indicated, increased shift costs have also been

378 observed in marmosets and rats with lesions to the medial PFC (Dias et al., 1996; Birrell and
379 Brown, 2000). Surprisingly though, rats with damage to the nucleus reuniens (Re), another
380 thalamic structure located near the MD, which interconnects the medial PFC and
381 hippocampus (Hoover and Vertes, 2007; Hoover and Vertes, 2011; Vertes et al., 2015) do not
382 cause deficits in the ED subtask or produce a significant ED shift cost. Instead, rats with NRe
383 damage are impaired at acquiring the attentional set strategy, similar to rats with ATN lesions
384 (Linley et al., 2016). Thus, our MD thalamus results are unique.

385 Other researchers using mice have proposed the MD supports the frontal cortex to
386 sustain intra-cortical attentional control without transferring categorical information about a
387 particular task rule (Schmitt et al., 2017), while others have shown medial PFC-MD
388 projections are important for behavioral flexibility but not task engagement (Marton et al.,
389 2017; Nakayama et al., 2018). Further, the MD has been shown to have a critical role in
390 maintaining the balance between excitation and inhibition in dorsomedial PFC via its
391 influence on interneurons (Anastasiades et al., 2021; Ferguson and Gao, 2018) and pyramidal
392 neurons (Collins et al., 2018; Delevich et al., 2015). Our results are supportive of these circuit
393 level interactions, although our deficits indicate the influence of MD on frontal circuits is
394 specific to certain aspects of the attentional set-shifting task, e.g. linked to the ED shift and
395 learning the optimal choice response strategy, but not to the ID shift or completing reversals.
396 However, our study involved permanent MD lesions, which are likely to have caused some
397 adaptations across the network, while the other studies likely involve short-term changes after
398 temporary inactivation of the MD. Nevertheless, it may be proposed that after MD
399 perturbations, while the animal is still able to detect a change in the task demands (i.e. they
400 are responsive to negative feedback), they are impaired at rapidly adapting their behavior and
401 coordinating correct choice responses after a change to the already established choice
402 response strategy (Block et al., 2007; Hunt and Aggleton, 1998). However, in both of these

403 studies, the deficits were attributed to increased perseverative responding. In contrast, our
404 current work and previous work in rhesus macaques has similarly shown an intact MDmc is
405 necessary for rapid reward guided learning of complex visual discriminations (Mitchell et al.,
406 2007a; Chakraborty et al., 2016; Chakraborty et al., 2019), although the deficits linked to
407 learning in monkeys are attributed to increased response switching (Mitchell et al., 2007a;
408 Chakraborty et al., 2016). These congruent results across species after MD damage suggest
409 that cortical information transfer via the MD is particularly important when 'on-the-fly'
410 changes in choice response strategies linked to establishing a new rule are required.

411 In addition, while the selectivity of the deficits after MD lesion are in some ways
412 comparative to medial PFC perturbations on attentional set-shifting, i.e. both have a
413 significant ED shift cost, our MD lesion rats also took more trials to criterion during the
414 simple discrimination (SD) subtask. Other studies also confirm MD lesion rats are impaired
415 in acquisition of an initial task rule (Hunt and Aggleton, 1998). Thus these results from
416 across species reinforce the notion that MD is not simply mimicking the PFC (DeNicola et
417 al., 2020; Miller et al., 2017; Mitchell et al., 2007; Mitchell and Gaffan 2008; Mitchell et al.,
418 2014). Consequently the influence of other cortico-cortical interactions that also indirectly
419 transfer information to the cortex via the MD and other thalamic structures, e.g. those PFC
420 interactions with limbic structures in the temporal lobes and sensory association areas must
421 also be important during learning sensory discriminations (Banjeree et al., 2020; Bueno-
422 Junior et al., 2018; Chakraborty et al., 2019; Floresco and Grace, 2003; Mitchell, 2015;
423 Pelekanos et al., 2020).

424 For the reversal subtasks (REV1 and REV2), surprisingly, MD lesion rats were
425 unimpaired during reversals in the reward contingencies. In contrast, rats or monkeys with
426 OFC perturbations are impaired in the reversal subtasks of the ID/ED task but conversely do
427 not show an ED shift cost (Dias et al., 1997; McAlonan and Brown, 2003; Chase et al.,

428 2012). MD is reciprocally connected to the OFC (Groenwegen, 1988; Preuss, 1995; Ray and
429 Price, 1992). Thus this double dissociation in deficits between these two reciprocally
430 interconnected brain regions needs to be reconciled. While previous evidence of reversal
431 learning deficits are reported in some tasks after MD lesion (Block et al., 2007; Chudasama et
432 al., 2001; Hunt and Aggleton, 1998; Ostlund and Balliene, 2008), the evidence is mixed
433 (Beracochea et al., 1989; Fresno et al., 2019). Our result and this evidence suggests the
434 information transfer between OFC and MD is not critical for reversal learning per se. Instead,
435 at least in monkeys, OFC-MDmc interactions are critical for adaptive, value based decision-
436 making (Browning et al., 2015; Izquierdo and Murray, 2010; Mitchell et al., 2007b).
437 Conversely, in rodent studies the OFC-striatal part of the cortico-striatal-thalamic neural
438 circuits are implicating in reversal learning (Gremel and Costa, 2013; Izqueirdo et al., 2017;
439 Nakayama et al 2018; Yang et al., 2020; Yin et al., 2005). Consequently other OFC-striatal-
440 thalamic and OFC-thalamic interactions are potentially involved in supporting reversal
441 learning. Thus far, it has been reported that thalamic inputs from the intralaminar thalamic
442 nuclei and motor thalamus to the striatum contribute a selective role in inhibitory control and
443 behavioral flexibility (e.g. Saund et al., 2017) and direct OFC connections to the submedius
444 thalamic nucleus contribute to updating action-outcome reversals (Fresno et al., 2019).

445 Intriguingly, our behavioral analyses showed that our MD lesion rats made fewer
446 correct 2nd choice responses. Given that MD lesion rats required more trials to criterion to
447 learn the SD and ED subtasks, this change in behavioral responses suggests that without the
448 MD thalamus, our rats could not rapidly adapt their initial choice responses after the changed
449 task demands. Interestingly though, this reduced correct 2nd choice responding does not
450 suggest the rats adopted perseverative responding or were not learning about the stimulus and
451 associated rewards. For example, after acquiring the ED shift, the MD lesion rats required
452 fewer trials to criterion to learn the final reversal, REV3. Instead, this facilitation of learning

453 during the final reversal subtask suggests that the rats had experienced 'overtraining' on the
454 stimulus features associated with each sensory dimension during learning the ED subtask
455 (Dhawan et al., 2019). As Pearce and Mackintosh (2010) propose, until learning is fully
456 consolidated, all stimulus features continue to be attended to and this is so for our rats even
457 with the MD lesion.

458 There may be other explanations for the SD and ED impairments observed in our MD
459 lesion rats. For example, with the ID/ ED task, it is important to establish that the animals
460 understand the relevant sensory dimension that is rewarded across the related subtasks within
461 the session. Fortunately, in our animals, this transfer of knowledge was evident as the MD
462 lesion rats showed reliable learning in the subtasks, CD, REV1, ID and REV2, that required
463 the implementation of choice responses (follow the same rule) to the same sensory dimension
464 as the SD to receive reward. Furthermore, both Sham controls and MD lesion rats showed
465 similar numbers of trials to criterion during the REV1 and REV2 subtask, which indicates
466 that they did not favor one feature of the stimulus dimension more than the other or that they
467 were insensitive to negative feedback. Finally, the MD is a subcortical node in the olfactory
468 neural circuitry that also includes the OFC (Courtiol et al., 2015; Veldhuizen et al., 2020).
469 However, evidence collected from rodents with MD perturbations or humans with strokes
470 affecting the MD indicates that changes to the MD do not impair olfactory discriminations
471 (Courtiol et al 2019; Tham et al., 2011). Moreover, our MD lesion rats showed similar levels
472 of olfactory discriminations as the MD Sham controls (see Material and Methods for further
473 details).

474 Finally, the reduced c-Fos counts in the OFC and medial PFC after MD lesion provide
475 additional support that MD-PFC interactions contribute to learning and cognitive flexibility.
476 Importantly, these changes highlight the diffuse influence of the MD thalamocortical inputs
477 to several frontal cortex structures (Alcaraz et al., 2016; Kuramoto et al. 2017; Mitchell,

478 2015; Wolff and Vann, 2019). Specifically, the reduction in c-Fos immunopositive counts in
479 the PrL, following MD lesion supports previous findings implicating medial PFC-MD
480 connectivity in flexible behaviors (Marton et al 2017; Nakayama et al., 2018). Furthermore,
481 the MD related reduction of c-Fos counts in the OFC provides additional evidence for the
482 contribution of this area in supporting online, 'here and now' reward guided learning and
483 decision-making (Gardner et al., 2017; Gardner et al., 2019; Schoenbaum et al., 2011; Wallis,
484 2007). Intact OFC connectivity is essential to the animals' ability to perform reward-guided
485 learning in order that other interconnected neural networks, likely including cortico-cortical,
486 cortico-striatal, and cortico-thalamo-cortical connectivity, can determine the optimal choice
487 responses and implement the appropriate actions (Browning et al 2015; Chakraborty et al
488 2016; Nakayama et al 2018; Rushworth et al., 2011).

489 The ID/ ED task is analogous to the Wisconsin Card Sorting Test (WCST) in humans.
490 In healthy humans performing the WCST during neuroimaging, the MD is activated during
491 responding to negative feedback after the choice has been executed (Monchi et al., 2001).
492 Unfortunately, thus far, humans with stroke damage in the MD have cognitive deficits that
493 are clinically very poorly defined (Pergola et al., 2018). However, people diagnosed with
494 Alzheimer's disease (AD), Parkinson's disease (PD), or schizophrenia show impaired
495 attentional set-shifting performance (e.g. Barch et al., 2009; Monchi et al., 2004; Owen et al,
496 1993). Neuroimaging and post-mortem studies show marked changes in the MD and/ or ATN
497 in these diseases (Hornberger et al., 2012; Ouhaz et al., 2018; Pergola et al., 2015; Perry et
498 al., 2018). Our current evidence advocates for studies investigating cortico-thalamocortical
499 transfer of information in people diagnosed with AD combined with more frontal pathology,
500 or PD, or schizophrenia.

501 To conclude, excitotoxic damage to the rodent central and medial MD selectively
502 increased the trials to criterion on the ED subtask, producing a shift cost. This selective

503 performance deficit is similar to monkeys with lateral PFC inactivation (Dias et al., 1996;
504 Dias et al., 1997) and rats with medial PFC lesions (Birrell and Brown, 2000). Further, this
505 dissociable deficit after MD lesion contrasts with monkeys or rats with perturbations to the
506 OFC, who are selectively impaired on reversal learning, but not on ED shifts (Chase et al.,
507 2012; Dias et al., 1997; McAlonan and Brown, 2003). As evidenced, the frontal cortex is
508 critically involved in value based decision-making and reward guided learning (Miller, 2000;
509 Rushworth et al. 2011; Wallis, 2007). However, cortico-thalamo-cortical connections also
510 contribute a role (Browning et al. 2015; Chakraborty et al., 2016; Izqueirdo and Murray,
511 2010; Mitchell et al., 2014; Pelekanos et al., 2020). In rodents, the MD and the medial PFC
512 together appear crucial for binding reward information and behavior (Bradfield et al., 2013;
513 Corbit et al., 2003), as inhibition of dorsomedial PFC-projecting MD neurons results in rats
514 having difficulties with tracking changes in action-outcome contingencies (Alcaraz et al.,
515 2018). In the current study, we show the rat medial and central MD is critical for
516 implementing and updating an optimal choice response strategy. That is, when the MD is
517 damaged, there is a diminished ability to rapidly learn a choice response strategy, as well as
518 update a well-established choice response strategy as task demands change within a session.
519 Reduced c-Fos expression observed in both the OFC and PrL support this evidence.
520 However, instead of increased perseverative errors as observed in other rodent studies with
521 MD lesions, our MD lesion rats made less correct 2nd choice responses, suggesting they were
522 unable to rapidly monitor and update 'on-the-fly' change of mind decisions when they
523 encountered the unrewarded stimuli on a given trial.
524
525
526 **4.0 Materials and Methods**

527 **Animals:** Twenty-five Lister hooded male rats weighing between 420 and 480 gm at time of
528 surgery (Charles River, UK) were group housed in a temperature and humidity-controlled
529 environment (21 ± 1˚C). The housing and husbandry compiled with the ARRIVE guidelines
530 of the European Directive (2010/63/EU) for the care and use of laboratory animals. Testing
531 was conducted in the light phase of a 12hr light/dark cycle (lights on at 7am). The rats were
532 maintained on a controlled feeding schedule (20 g/rat/day) with water freely available in the
533 home cage. All experimental procedures were performed in compliance with the United
534 Kingdom Animals (Scientific Procedures) Act of 1986. A Home Office (UK) Project License
535 authorized to Dr AS Mitchell licensed all procedures after review by the University of Oxford
536 Animal Care and Ethical Review committee and Home Office Inspectorate.
537 **Surgery:** Rats were anesthetized by isoflurane and oxygen mix (4% induction, 1.8–2%
538 maintenance), and given analgesia in subcutaneous injections of 0.05mg/kg buprenorphine
539 (Vetergesic; 0.3 mg/ml) and 1 mg/kg Metacam (Meloxicam; 5 mg/ml). Rats were secured in
540 a stereotaxic frame (Kopf) with atraumatic ear bars and the nose bar set to +3.3 mm to
541 achieve a level skull. A subcutaneous injection of 2 mg/kg bupivacaine (Marcaine; 2.5
542 mg/ml) was administered into the scalp in the location of the midline incision. Viscotears was
543 applied to keep the eyes moist. During surgery, each rat was placed on a heat pad and
544 covered in bubble wrap with an internal rectal thermometer probe to monitor and maintain
545 normal body temperature. Warmed sterile saline (1 ml/100 gm) was administered
546 subcutaneous into the scruff of the neck after one hour. A midline incision was performed.
547 Bregma and lambda coordinates were determined. A dental drill with a trephine head was
548 used to create a craniotomy over the midline. To maximize lesion accuracy, anterior and
549 posterior injection sites were calculated from Mitchell et al. (2005) according to the bregma–
550 lambda distance in each rat. Coordinates were for anterior MD injection: anterior–posterior
551 (AP) = – 0.395 mm, medial-lateral (ML) = – 0.1 (avoiding the superior sagittal sinus, which

552 was visible within the dura inside the craniotomy) and dorsal-ventral (DV) = 0.56 mm (from
553 dura), volume of excitotoxin = 0.20 µl; for posterior MD: AP = – 0.435 mm, ML = + 0.1 and
554 DV = 0.57 mm (from dura), volume of excitotoxin = 0.18 µl. Fifteen rats (MD lesion)
555 received 0.12M of NMDA (N-methyl-D-Aspartate) dissolved in phosphate buffer (pH 7.20)
556 in each hemisphere from a 1 µl-gauge Hamilton bevelled-tip syringe. The injections were
557 performed manually, taking 3 min each, and after injection the needle was left in situ for a
558 further 3 min to allow diffusion and to limit wicking of the NMDA. A further 10 rats (MD
559 Sham controls) received injections of sterile phosphate buffer instead of NMDA using the
560 same injection coordinates. Injections were given bilaterally in the MD. Upon completion of
561 surgery, wounds were sutured with Vicryl 4.0. Rats were housed singly during recovery for
562 up to three days and were then returned to their pre-surgery housing cohort. Postoperative
563 oral analgesia, 1mg/kg Metacam (Meloxicam, 1.5 mg/ml) dissolved and set in jelly was
564 provided in individual bowls to each rat daily for three days. Behavioral and physiological
565 evidence showed that all rats recovered well, with normal eating and pre-surgery weights
566 returning within 24h. Food regulation (20 gm/day/rat) started again 10 d after recovery.
567 Postoperative testing began at least 15 d after surgery. The researcher was blind to the lesion
568 group of each animal until all tests were completed.

569 **ID/ED Attentional Set Shifting paradigm**

570 **Apparatus:** The test chamber consisted of a modified Plexiglass home cage (40 × 70 × 18
571 cm) with Perpex dividers separating the cage into a large start chamber (40 × 46 cm) and two
572 identically sized (24 × 20 cm) choice chambers to which access was controlled by removable
573 Perspex doors. The digging bowls were ceramic (internal diameter 7 cm, depth 4 cm) and
574 were placed within the choice chambers. The bowls were filled with digging media of
575 different textures, and the digging media were scented with different spices (see **Table 1** for
576 the examples used). The odor or digging media discriminations, pairs of stimuli used, and the

577 correct stimulus within pairs were counter-balanced across subtasks and matched between
578 groups. The bowls were baited with Honey Nut Cheerios (Nestle®), each bowl contained a
579 hidden (securely fixed under a metal grid) Honey Nut Cheerio to serve as an odor mask.
580 During testing, only one of the bowls was baited and rats determined which bowl was baited
581 using either the texture of the digging medium or the odor as cues. Prior to testing, rats were
582 taught to dig in bowls filled with home-cage bedding material to retrieve one half of a Honey
583 Nut Cheerio. The task was performed as previously described in Birrell and Brown (2000)
584 and divided into two phases administered on two consecutive days.

585

586 **Table 1. Sensory dimensions (odors and digging media) and stimulus features (O1–O6;**
587 **M1–M6) used in the ID/ED attentional set-shifting task.**

Odors		**Digging media**	
O1 - Cinnamon	O2 - Ginger	M1 – Coarse tea	M2 – Fine tea
O3 - Sage	O4 - Paprika	M3 - Sand	M4 - Grit
O5 - Turmeric	O6 - Cloves	M5 - Coarse shavings	M6 – Fine shavings

588

589 **Training:** On the day before testing, each rat learnt one simple two-choice discrimination
590 (SD) using either of the two sensory dimensions: odor (mint vs oregano), or digging media
591 (shredded paper vs cotton pads), to a criterion of six consecutive correct trials. The rewarded
592 odors or digging media were counterbalanced across the two groups, and these exemplars
593 were not used again throughout testing. Digging was defined as active digging with both
594 front paws or active foraging with the snout in the digging media. Sniffing or touching the
595 media with the paws was not scored as a dig.

596 **Testing paradigm:** The following day, each rat was given a series of seven two-choice
597 discriminations (subtasks) in the following order: a new simple discrimination (SD) using
598 either of two sensory dimension (odor or digging media); a compound discrimination (CD)
599 using the same rewarded sensory dimension and two-choice discrimination as the SD,
600 combined with the other irrelevant sensory dimension; first reversal (REV1), in which the
601 exemplars remained the same as in the CD but the correct (rewarded) and incorrect
602 exemplars were reversed; intra-dimensional shift (ID), in which new exemplars were used,
603 but the relevant sensory dimension remained the same as in the previous subtasks; second
604 reversal (REV2), where exemplars in the ID remained the same but the reward contingencies
605 of the two exemplars were reversed; extra-dimensional shift (ED), where new exemplars
606 were used and the previously irrelevant sensory dimension becomes relevant; and a third
607 reversal (REV3), where exemplars in the ED subtask remained the same but the reward
608 contingencies of the two exemplars were reversed.

609 The task is self-paced and relies on the natural foraging behaviors of the rats. The first
610 five two-choice discrimination subtasks (SD, CD, REV1, ID, REV2) must be solved by
611 discriminating between exemplars from the same sensory dimension. In this stage of the task,
612 the rat is rewarded for choices based on specific perceptual features of the stimuli, while
613 ignoring other features that also distinguish the stimuli. After acquiring each set of two-
614 choice discriminations to a performance criterion of six correct consecutive trials, the rats
615 encounter a reversal of the reward contingencies associated with the exemplars (a reversal
616 subtask: REV1 and REV2). For the final two subtasks (ED and REV3), exemplars from the
617 previously irrelevant sensory dimension become relevant. Therefore the rat must shift its
618 attention (and adjust its choice response strategy) to the previously irrelevant sensory
619 dimension and perceptual feature to receive reward (ED subtask). The attentional set-shfiting
620 cost is calculated by comparing trials to criterion during the intra-dimensional shift, where

621 the sensory dimension is consistent with previous subtasks, and the extra-dimensional shift,
622 where the now relevant sensory dimension had been previously ignored and thus requires a
623 shift to optimise continuing to retrieve rewards.

624 **Odor detection test:** At the completion of ID/ ED testing, the olfactory abilities of the rat to
625 smell the odor of the buried half-Honey Nut Cheerio were assessed. This task consisted of 10
626 consecutive trials where the rat was exposed to bowls containing similar bedding. The rat was
627 placed in the waiting area of the set-shifting apparatus. Similar bedding-filled bowls were
628 placed, one in each of the choice chambers, only one bowl contained half a Honey Nut
629 Cheerio at the bottom (pseudorandomly assigned to avoid the rat developing a response
630 strategy). The barrier was raised, allowing the rat access to both bowls. The rat had to chose
631 to dig into one bowl and had up to 15 minutes to make a digging response on each trial. If the
632 rat dug in the correct bowl, the trial was recorded as correct and the rat was returned to the
633 waiting area and the barrier lowered to block access to both choice chambers. If the rat dug in
634 the incorrect bowl, the trial was marked as incorrect. The rat was permitted to continue to
635 explore the incorrect bowl; the trial was terminated when the rat returned to the waiting area.
636 In all cases, the ability of each rat to detect the reward location was no different to chance
637 guessing.

638 **c-Fos immunohistochemistry:** After completion of either the SD or ED subtasks, the rats
639 were placed in a dark holding environment for 90 minutes before being deeply anaesthetized
640 with sodium pentobarbital (Euthanol 1.0 ml/rat, 200 mg/ml: Merial, Harlow, UK), and
641 perfused transcardially with 0.9% (w/v) saline and 4% (w/v) paraformaldehyde in 0.1M
642 phosphate buffered saline (PBS). Brains were then removed and post-fixed overnight (4˚C),
643 then incubated using 30% (w/v) sucrose in 0.1M PBS over 48h (4˚C). Free floating sections
644 (40 µm) were cut on a freezing microtome, the slices were then preserved in cryoprotectant

645 (0.1M PBS containing 24% (v/v) glycerol and 24% (v/v) ethylene glycol) and stored at
646 −20°C until processing for immunohistochemistry.

647 Sections containing frontal cortex were processed to assess the expression of the
648 immediate early gene *c-Fos* in the prelimbic (PrL) and OFC. After being removed from the
649 −20°C freezer, free floating sections were washed three times, for 10 minutes each, in 0.1M
650 phosphate buffered saline containing 0.2 % (v/v) Triton X-100 (PBS-Tx). Following
651 washing, non-specific binding was blocked by incubating the sections in 20% (v/v) normal
652 goat serum (NGS) in PBSTx for an hour at room temperature with gentle agitation. Sections
653 were then incubated in the primary antibody (rabbit antibody to human c-Fos: Catalog
654 #ABE457, Merck Millipore, 1:1000) in PBSTx with 1% (v/v) NGS for 48h at 4˚C. Sections
655 were then washed three times for 10 minutes each in PBSTx and then incubated, for four
656 hours in the dark at room temperature, in the secondary antibody (goat anti-rabbit IgG,
657 Cyanine3, Catalog #A-10520, Thermo Fisher, 1:1000) in PBSTx containing 1% (v/v) NGS.
658 Sections were washed three times for 10 mins in PBS before being mounted to glass slides
659 and cover slipped using VECTASHIELD (Vector Laboratories, Catalog #H-1200-10)
660 containing DAPI, a DNA stain to visualise cell nuclei. The slides dried and were then stored
661 in the dark at 4°C until visualized.

662 **Immunohistochemical data collection:** *Identification of regions of interest:* The slides
663 containing the two areas in frontal cortex: PrL and OFC cortex were determined according to
664 the atlas of Paxinos and Watson (2008). Confocal images were acquired with an
665 LSM880/Axio.Imager Z2 (Zeiss) the 20x objective was used and all imaging settings (laser
666 %, pinhole/optical section, pixel size, gain, and scanning speed) were kept constant between
667 animals. All cell counts were conducted blind to the experimental group. Cell counting and
668 image analysis were performed with a computer-assisted image analysis system (Neurolucida
669 Software, MicrobrightField). Double counting of the same cell was minimized using thin

670 sections (40 µm) and non-consecutive section collection (every fourth section). Three
671 bilateral sections per brain region per animal were counted and averaged to give the number
672 of c-Fos immunopositive cells. An analysis of the number of immunopositive cells was
673 determined using Abercrombie's formula (Abercrombie, 1946): $p = (1/f)\ AM/\ (D + M)$,
674 where p is the total number of positive stained cells in the region of interest, f is the
675 frequency of the selected sections used for immunostaining (1/4), A is the gross cell count, M
676 is the thickness of the sections (40 µm), and D, (20 µm) is the average diameter of cell nuclei.
677 The same counting procedure was applied to both groups. Unbiased stereology was not used
678 in this study, so the results reported here represent relative, not absolute changes in c-Fos
679 immunoreactivity. The researchers were blinded to the photos that were being processed.

680 **Lesion extent:** Photomicrographs of the Nissl-stained MD sections were captured using a
681 camera mounted on a freestanding Leica DMR microscope (Leica Microsystems) using a
682 1.6× objective so that the whole section could be visualised in the photomicrograph. MD
683 volumes were measured using the NIH software ImageJ (http://rsbweb.nih.gov/ij/). In each
684 rat, the intact MD volume from both the left and the right hemisphere was assessed. The final
685 reading was calculated according to the Cavalieri principle (Regeur and Pakkenberg, 1989)
686 and expressed as the percentage of MD Sham controls.

687 **Behavioral data analysis:** In the behavioral experiments, all rats performed a preoperative
688 and postoperative session, and they completed the seven two-choice discrimination subtasks
689 in an identical order. Data are expressed as mean and standard deviation. Postoperative mean
690 trials to criterion, shift cost, percent correct 2nd choice responses, and reaction time (seconds)
691 were analysed using repeated measures ANOVAs with Stage (comprising the 7 subtasks) as
692 the within-group repeated measure and Lesion_type (MD lesion or MD Sham control) as the
693 between-group factor. For significant interactions, posthoc simple main effects analyses were

performed using additional two-way ANOVAs for repeated measures (e.g., ID/ED shift) or independent t-tests for relevant subtasks (corrected for multiple comparisons). All statistical analyses were calculated using SPSS 24 software. The significance level was set at $p < 0.05$.

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