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Abstract

We explored here the hypothesis that temporary chronic water restriction in mice affects social behavior, via its action on the density of 5-HT neurons in dorsal and median raphe nuclei (DRN and MRN). For that, we submitted adult C57BL/6J mice to mild and controlled temporary dehydration, i.e., 6h of water access every 48h for 15 days. We investigated their social behavior in a social interaction task known to allow free and reciprocal social contact and to rely on prefrontal cortex activity and monoaminergic prefrontal input. Results showed that temporary dehydration increases significantly time spent in social contact and social dominance. It also expands 5-HT neuron density within both DRN and MRN and the behavioral and neuronal plasticity were positively correlated. Our findings suggest that disturbance in 5-HT innervation caused by temporary dehydratation stress unbalances choice processes of animals in social context.

Keywords: Raphe nucleus; Serotonin; Dehydration; Social behavior; Immunohistochemistry.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Acknowledgments

Introduction

In the wild, rodents are able to survive on relatively dry diets and may go into temporary dehydration states for various periods (Tirado et al., 2008). Temporary dehydration alters serotonergic innervation in multiple mammal species such as rats (Chatoui et al., 2012), merions (Elgot et al., 2009; 2012$_{a, b}$), and gerbils (Boukersi et al., 2018). A temporary controlled dehydration in the laboratory is thus an ecological modulator of serotonin activity that mimics what happens in real life context. Serotonin (5-hydroxytryptamin or 5-HT) is the most widely distributed transmitter in the brain (Dahlstrom and Fuxe, 1964) and is well known for its role in mood regulation (David and Gardier, 2016) since abnormalities in its neurotransmission are associated with neuropathologies like depression and anxiety (Cowen, 2008; Quesseveur et al., 2013) and other neurological or psychiatric disorders (Jayamohanan et al., 2019). However, it is still unclear how various environmental factors such as temporary dehydration can physiologically control brainstem neuromodulatory systems, including the dorsal and medial raphe (DRN and MRN) serotonergic nuclei, the main sources of 5-HT (Michelsen et al., 2008; Steinbusch, 1981). It is well established that 5-HT containing neurons of DRN and MRN project to forebrain areas (Kosofsky and Molliver, 1987; O'Hearn and Molliver, 1984; Steinbusch and de Vente, 1997) and receive descending projections from forebrain regions (Celada et al., 2001; Peyron et al., 1998).The MRN innervates several subcortical areas such as the hippocampus and the nucleus accumbens, and sends axons to dopaminergic (DA) neurons of the ventral tegmental area which in turn innervates the prefrontal cortex (PFC). The DRN innervates the PFC, the amygdala, the nucleus accumbens and the hippocampus and sends axons to DA neurons of the substantia nigra that innervate the amygdala and the dorsal striatum. Both DRN and MRN innervate several hypothalamic nuclei, therefore triggering endocrine release (Lechin et al., 2006). The 5-HT system is thus ideally placed to support integration of emotional, motivational and cognitive behaviours (Muzerelle et al., 2014; Suri et al., 2015). For example, in animal models, 5-HT in limbic forebrain areas was altered by multiple environmental stressful conditions, such as temperature variation (Linthorst et al., 2008), swim stress (Kelly et al., 2011), or social defeat (Paul et al., 2011). In humans, patients with anxiety and affective disorders show an increase of brain 5-HT turnover compared to healthy subjects (Esler et al. 2007; Barton et al. 2008). However, there are little studies reporting alteration of serotonergic innervation in 5-HT main source of production, namely DRN and MRN.

Social interactions are important components of healthy behaviours (Monica et al., 2017) since they enable animals to communicate with and learn from one another, and can increase the likelihood of survival and reproduction (Ferri et al., 2016). We previously showed that social interaction relies on PFC integrity and triggers its activation (Avale et al., 2011; Nosjean et al., 2018), and that both cholinergic integrity (de Chaumont et al., 2012; Nosjean et al., 2015) and the PFC monoaminergic input are necessary for displaying adapted and non aggressive reciprocal social interaction (Coura et al., 2013). A recent study provides proteomic evidences that serotonergic and dopaminergic activities were increased by social play in rats (Alugubelly et al., 2019). In addition, dorsal raphé activation was specifically associated with social dominance (Kim et al., 2015) while optogenetic stimulation of dorsal raphé nuclei elevated prefrontal 5-HT levels along with social behavior frequency (Balazsfi et al., 2018). Despite these recent data, the precise role of serotonergic activity on social behavior remains largely unknown.

In this study, we tested the behavioral and neurobiological consequences of dehydration on social behavior and on DRN and MRN neuronal reactivity.

Materials and methods

Animals

20 adult male C57BL/6J mice obtained from Charles Rivers Laboratories (L'Arbresle Cedex, France) were used in our study. We randomly divided them into three groups: the first group (n=5) served as a control with water access *ad libitum*, the second group (n=5) was submitted to a controlled dehydration protocol by allowing them water access only for 6 hours per 48 hours for15 consecutive days, the third group (n=10) was used as social partner (see below) and had access to water and food *ad libitum*. All animals had food access *ad libitum*.

Animals of groups 1 & 2 were socially isolated for 4 weeks prior to social tests (transparent plexiglas cage, 50x20 cm, covered with clean sawdust) while animals of group 3 were maintained 3 to 5 per cage under constant room temperature (23±2°C), humidity and 12/12 h light-dark cycle.

Behavioural procedures were carried out in accordance with European Commission guidelines. All efforts were made to minimize animal suffering and reduce the number of animals used.

Social interaction task (SIT)

At the end of the dehydration procedure, we followed the experimental protocol previously described for social interactions (Avale et al., 2011; Nosjean et al., 2015). Briefly, each

isolated mouse (thereafter called host mouse) was put in a novel transparent open field (50 x20 cm) containing a handful of clean sawdust, where it stayed alone exploring this novel environment for 30 minutes. This procedure promotes the development of limited dominance from the host mouse (De Chaumont et al., 2012; Faure et al., 2017; Nosjean et al., 2015). After that, a visitor male mouse of the same strain and age and not isolated before (maintained in social cages of 3 to 5 animals), was introduced into the open field for a 8-min social interaction test that was recorded by a camera connected to a computer for offline analysis.

We scored the time spent in contact, the number of follow behaviors (i.e., bouts of behaviors during which the host mouse follows the visitor mouse while making nose-genital contact), the number of escape behavior (i.e. behavioral sequences initiated by the host mouse consisting of interrupting the social contact and going away from the visitor mouse) and the number of rearing (lifting the two forepaws) performed by host mice.

Tissue preparation and immunostaining for 5-HT

At the end of the experiment, as previously described (Nosjean et al., 2015; Boukersi et al., 2018), all mice were deeply anesthetized by intraperitoneal injection of sodium pentobarbital (40 mg/kg and transcardially perfused with ice-cold phosphate buffered saline (PBS, 0.1 M, pH 7.4) followed by 4% paraformaldehyde in (PBS, 0.1 M, pH 7.4). Brains were removed and post-fixed for one week in the same fixative at 4 °C. For each brain serial coronal sections (40µm thickness), including the raphe nuclei in the brainstem were cut using Leica vibratome. Free floating sections were collected in 6-well tissue culture plates in 1.5 ml of cryoprotection solution and stored at -20°C until the day of primary antibody incubation. Sections processed in midbrain through the DRN and MRN were chosen for 5-HT immunolabelling. Free-floating sections from both hydrated and dehydrated groups were immunostained simultaneously using the same reagents and same incubation time. Free-floating sections were rinsed 3 times in (PBS, 0.1 M) before being incubated in a solution containing methanol and hydrogen peroxide during 30 minutes at room temperature, rinsed in 0.1 M PBS followed by one wash in (PBS, 0.1 M) containing 0.2% Triton X-100 (PBST), and preincubated in 5% normal goat serum with PBST for 1 h. Sections were then incubated overnight at 4°C with rabbit primary antibody anti 5-HT (Euromedex) diluted 1:2000 in PBST and goat serum 5%. The next day tissues were washed 3 times in PBST the incubated for 2 h in goat secondary biotinyled anti-rabbit IgG (Eurobio) diluted 1:200 in PBST and goat serum 5%. Tissue was then washed 3 times in PBST followed by 2 h incubation with an avidin-biotin-peroxidase complex (ABC, Vectastain ABC kit, Vector laboratories). After washing sections in BPST

then twice in Tris HCL 0.1 M, the peroxidase activity was revealed by incubating them in 0.03% DAB (3,3' diaminobenzidine, Sigma) + Nickel ($NiCl_2$) 0.06% and 0.02% H_2O_2 in 0.05 M Tris HCl, pH 7.5. All immunochemical reactions and washings described above were possessed simultaneously in four 12-well tissue culture plates, 10 sections in each well, to insure identical condition staining for all sections. Immediately after the chromogen reaction, sections were washed in (PB, 0.1M) and then in 0.15% gelatine in H_2O before being mounted on glass microscope slides (Thermo Scientific Super Frost Plus). Lastly, slides were air dried for 24 hours, dehydrated through 2 min serial ethanol baths (70%, 95% and 100% ethanol), and cleared with xylene. Coverslips were placed on the sections using Eukit for optic microscopy observation.

5-HT immunostaining assessment

The selected coronal brain sections permitted evaluation of raphe regions known to be heavily populated with serotonergic neurons. Anatomical landmarks were used to ensure that comparable brain sections were analyzed for each region in each animal. Using atlas brain of mouse (Paxinos and Franklin, 2001), three sections corresponding to the same three levels of bregma (-4.72, -4.60 and -4.48) were chosen for each brain in which the whole DRN and MRN could be seen clearly and most entirely. Examination of the slices was performed by Olympus light microscope coupled to an image-analysis workstation (Mercator; Explora Nova software). Photomicrographic digital images were taken for the three sections of each animal's brain, and the average density of 5-HT immunopositive neurons (number of somas per $1mm^2$) was calculated in DRN and in MRN by counting automatically all neurons having colour density more than threshold defined at start of counting.

Statistical analysis

Because of the small number of animals in each group (n=5), Mann-Whitney test was chosen to compare results of hydrated and dehydrated groups. A p value <0.05 was considered to indicate statistical significance between groups. Finally, to examine potential relationships between SIT and 5-HT immunostaining we applied the non-parametric test of correlation of Spearman, considering a significant correlation at p<0.05.

Results

Effect of water restriction on social interaction task

Our data showed an increase of time spent in social contact betwen animals in dehydration condition as compared to normal hydratation (p= 0.015) (Fig 1). The number of follow

behavior, index of social dominance, was significantly higher in the dehydrated group as compared to normally hydrated one (control) (p= 0.007) (Figure 1). The number of rearings and of escape behavior were not significantly altered in dehydrated animals (group effect respectively p= 0.221 and p= 0,149).
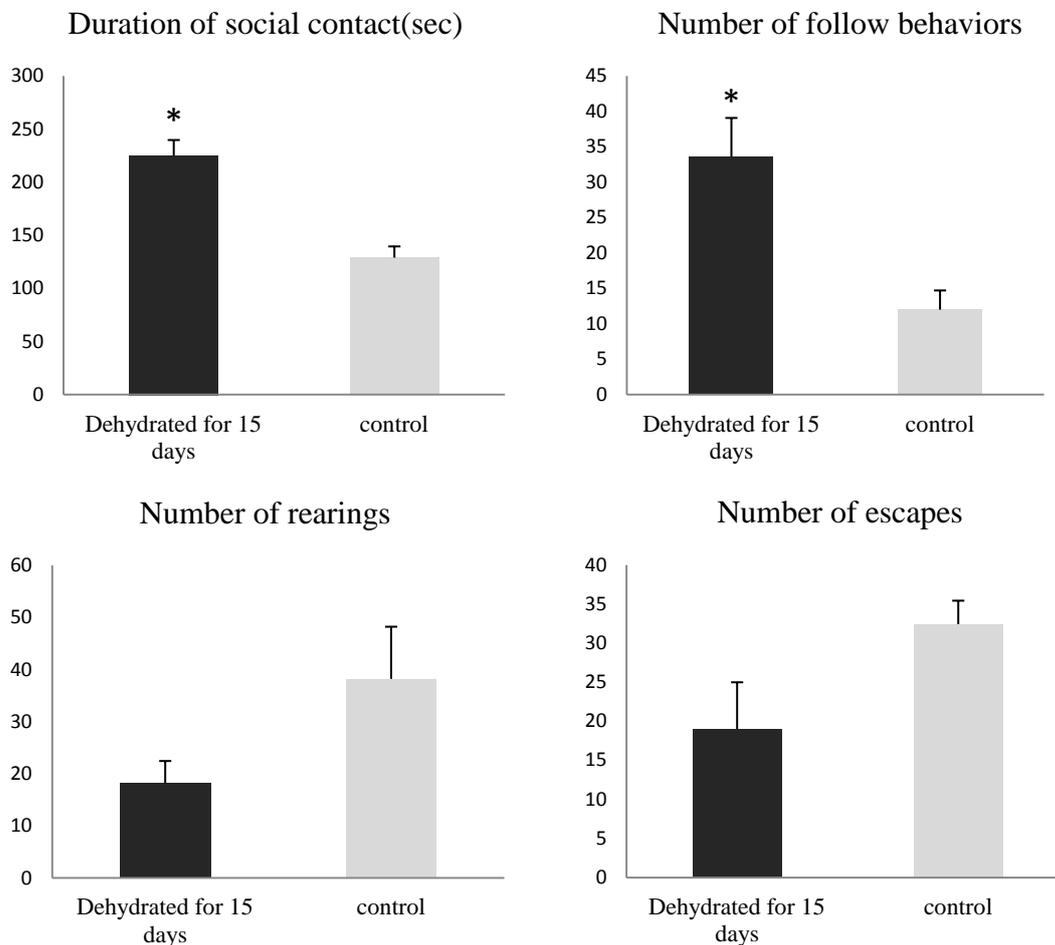
Figure 1. Social interaction task in dehydrated and control mice. Data is presented as means ± SEM. Significant group effect (i.e. effect of dehydration) is indicated by * (p< 0.05, Mann-Whitney test).

Serotonin immunolabeling in DRN and in MRN

We examined the 5-HT immunolabeling in the DRN and MRN. Positive 5-HT immunolabeled neurons density in both nuclei was significantly increased in dehydrated mice as compared to controls (p= 0.007 and p= 0.015, Figures 2 and 3)
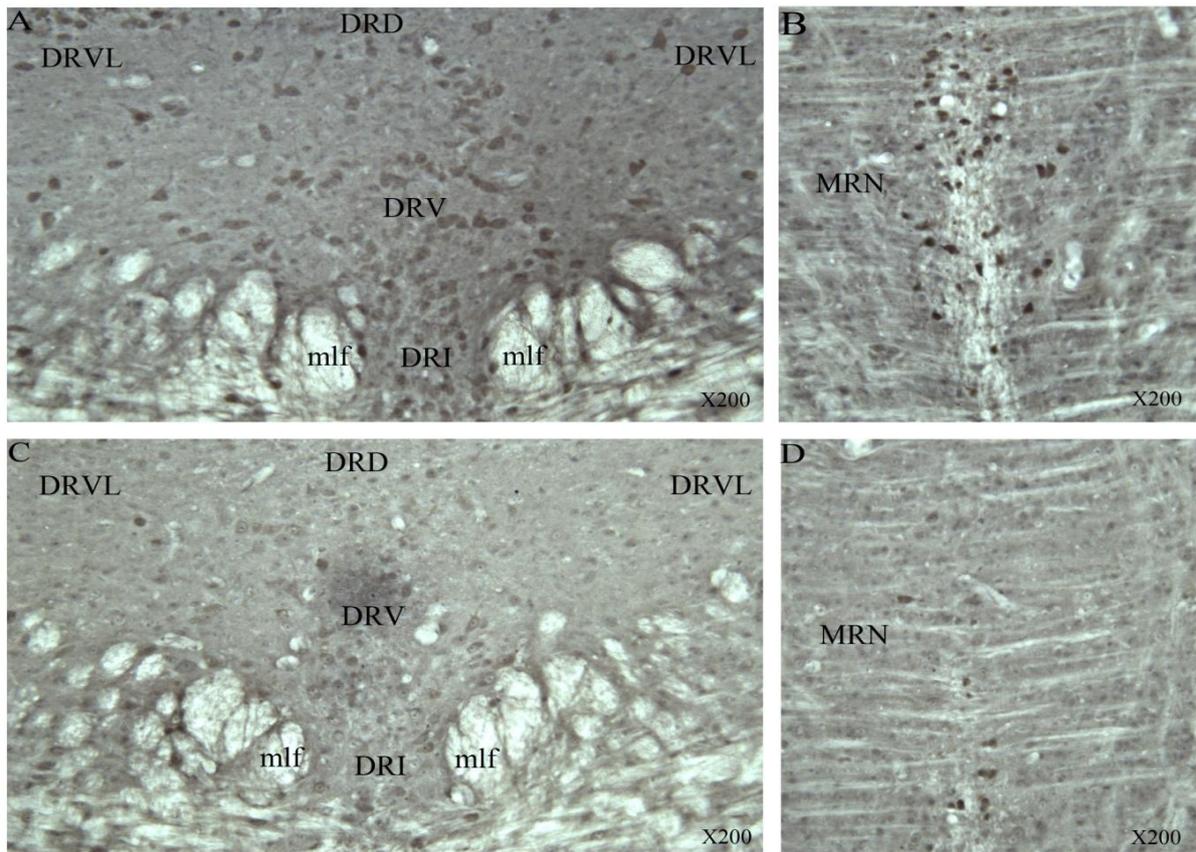
Figure 2. Representative microphotographs of 5-HT immunolabeled neurons in the dorsal raphe nucleus (DRN, A & C) and median raphe nucleus (MRN, B & D, bregma -4.72 mm) in dehydrated (top) and control mice (bottom). DRD: dorsal part of dorsal raphe nucleus; DRVL: ventro lateral part of dorsal raphe nucleus; DRV: ventral part of dorsal raphe nucleus; DRI: interfascicular part of dorsal raphe nucleus; mlf: medial longitudinal fasciculus.
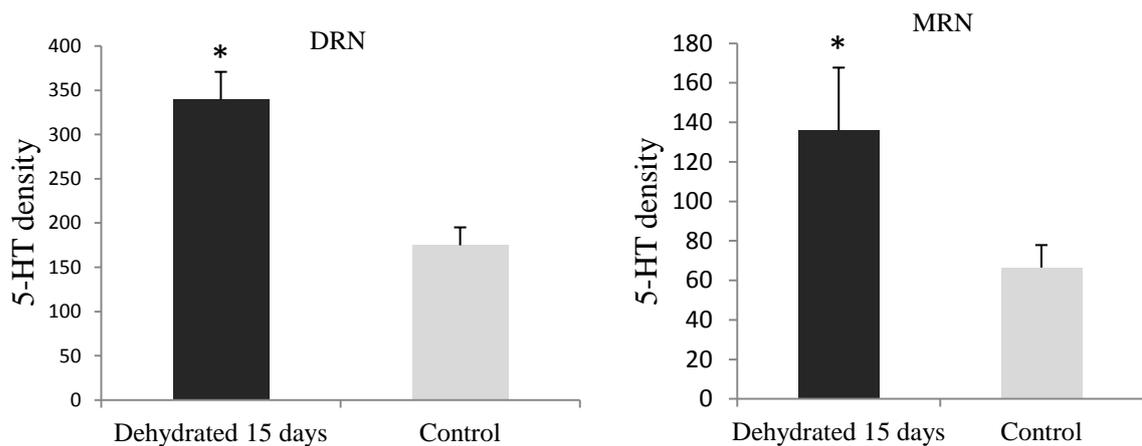

Figure 3. 5-HT immunolabeled neuron density in the DRN and MRN in dehydrated and control mice. Data is presented as means ± SEM. Signficant group effect (i.e. effect of dehydration) was indicated by * (p< 0.05, Mann-Whitney test).

Correlation between serotonin immunolabeling in DRN and MRN and social behavior in SIT

Across both DRN, density of 5-HT immunolabeled neurons correlates positively and significantly with time spent in social contact ($R^2 = 65\%$; $p < 0.01$, Figure 4) and number of follow behaviors ($R^2 = 65\%$; $p < 0.01$, fig 5). However, in MRN, density of 5-HT immunolabeled neurons correlates positively and significantly only with time spent in social contact ($R^2 = 52\%$; $p < 0.05$, Figure 4) but not with the number of follow behaviors ($R^2 = 41.5\%$; $p > 0.05$, fig.5). The density of 5-HT neurons in DRN and MRN was not correlated with the number of escape behavior ($R^2 = 5.9\%$; $p > 0.05$ and R^2 56.8%; $p > 0.05$ respectively, Figure 6) nor with the number of rearings ($R^2 = 3.1\%$; $p > 0.05$ and $R^2 = 42.1\%$; $p > 0.05$ respectively, Figure 7).
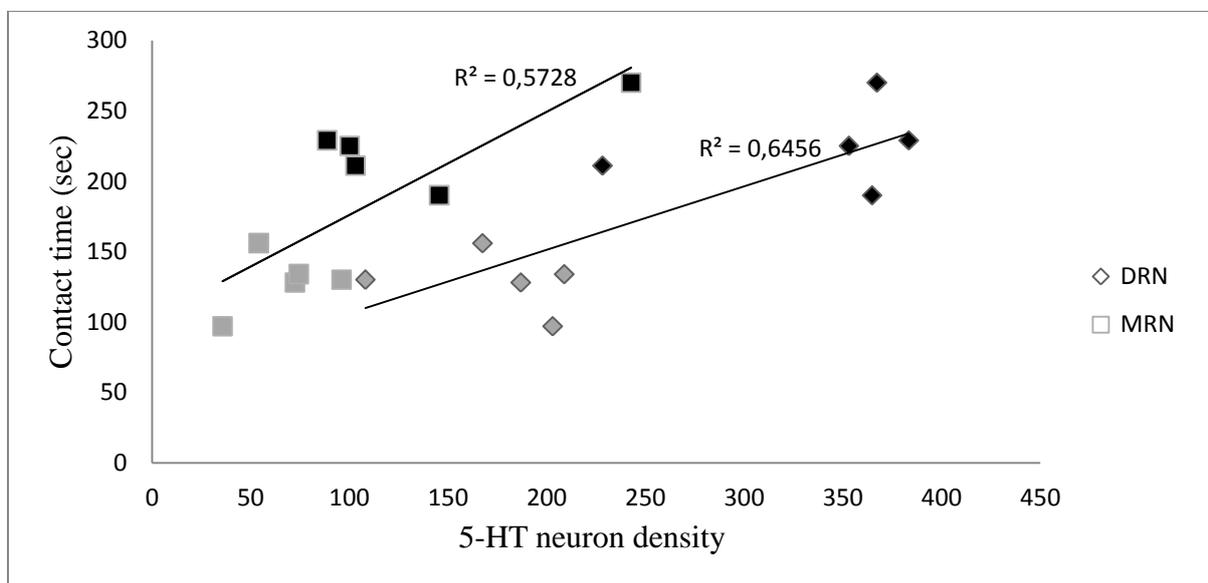
Figure 4. Positive correlation between 5-HT neuron density in the DRN and MRN and contact time in the social interaction task. Black dots represent dehydrated mice, grey dots represent control mice. Significant correlation was indicated by * ($p < 0.05$, R^2 Spearman correlation coefficient).
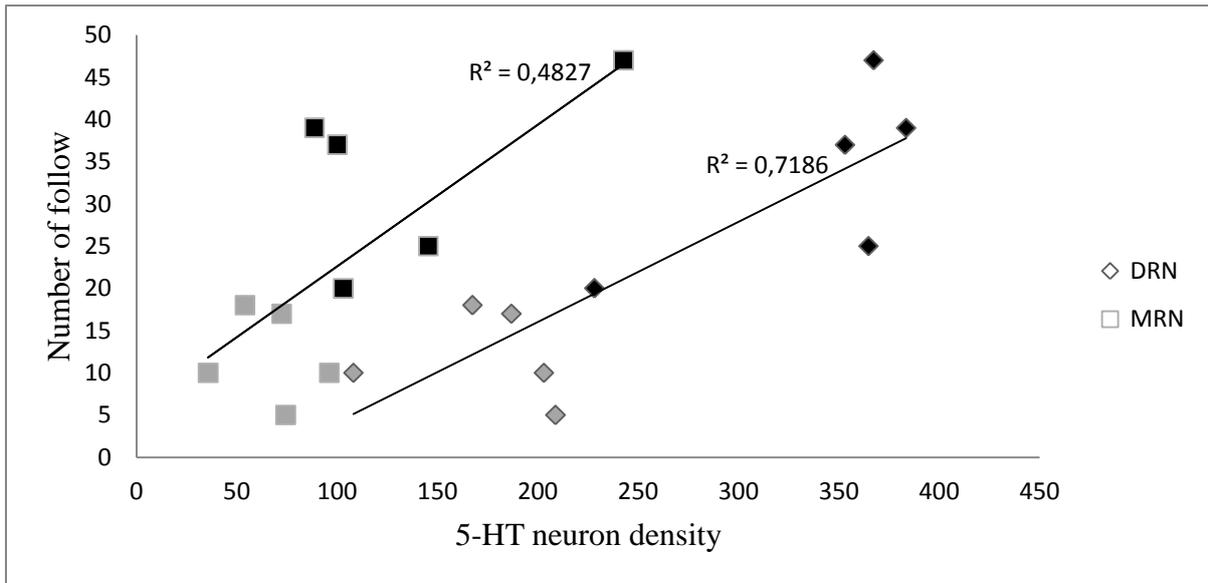
Figure 5. Positive correlation between 5-HT neuron density in the DRN and MRN and the number of follow behaviour displayed by the host mice. Black dots represent dehydrated mice, grey dots represent control mice. Significant correlation was indicated by* ($p < 0.05$, R^2 Spearman correlation coefficient).
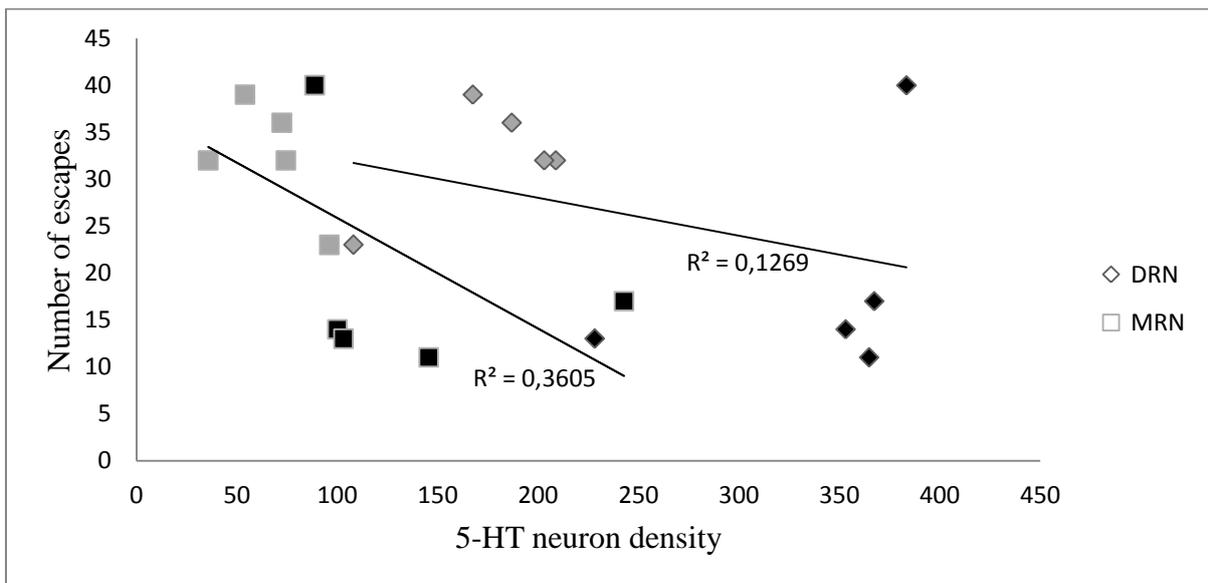
Figure 6. No correlation between 5-HT neuron density in the DRN and MRN and the number of escapes displayed by the host mice. Black dots represent dehydrated mice, grey dots represent control mice ($p > 0.05$, R^2 Spearman correlation coefficient).
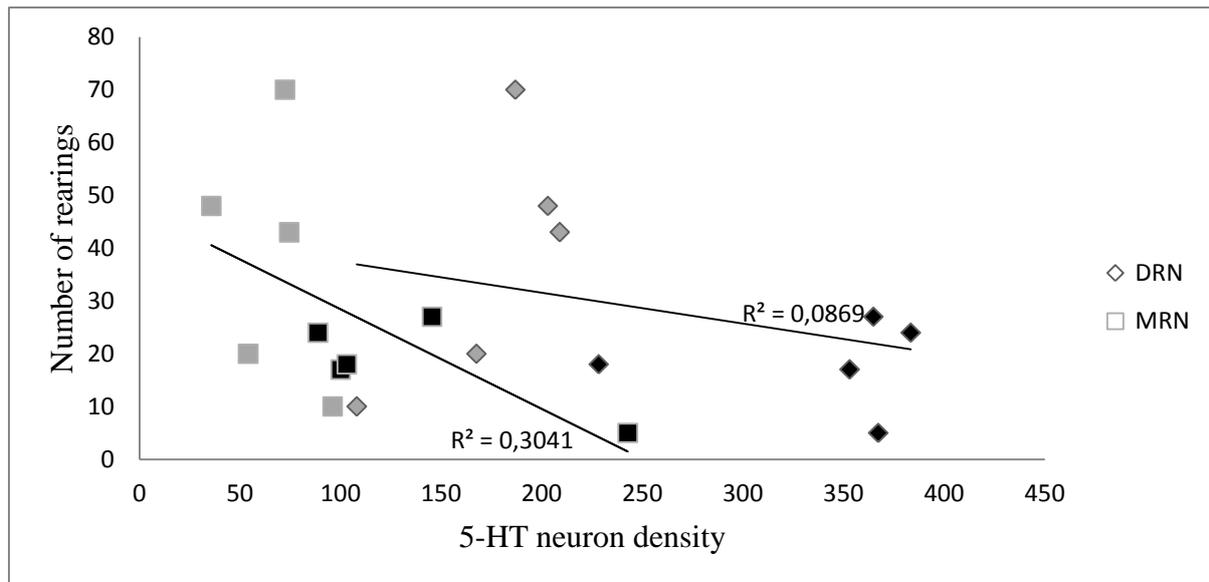
Figure 7. No correlation between 5-HT neuron density in the DRN and MRN and the number of rearings displayed by the host mice. Black dots represent dehydrated mice, grey dots represent control ($p > 0.05$, R^2 Spearman correlation coefficient).

Discussion

In the present study, we aim to explore the hypothesis that temporary chronic water restriction could affect social behavior, via its action on the density of 5-HT neurons in DRN and in MRN. The C57Bl/6j strain that we used is known for its sociability and is thus perfectly suitable for studying social behavior (Faure et al. 2017; Lawrence et al. 2017).

Results reveal significant increases of the time spent in social contact and of dominance behavior, and of 5-HT neurons density within both DRN and MRN in dehydrated animals as compared to control animals.

Our findings suggest that disturbance in 5-HT innervation caused by temporary dehydratation stress could unbalance choice processes of animals in the social task. Indeed, we previously showed that this social task relies on the ability to make choices between two concurrent motivations, i.e., getting a social contact and exploring a novel environment (Granon et al., 2003; Avale et al., 2011; De Chaumont et al., 2012;), processes supported by prefrontal activity (Avale et al., 2011; Nosjean et al., 2018) and prefrontal monoaminergic modulation (Cambon et al., 2010; Coura et al., 2013). Results of correlation between 5-HT immunolabling in DRN and MRN and social contact parameters support this hypothesis, showing that higher number of 5-HT neurons in DRN and MRN is associated with longer

social contact and more dominance behavior. We previously evidenced that follow behavior, an index of social dominance, largely contributes to social contact (Coura et al., 2013; Faure et al., 2017) and is promoted by acute stress (Nosjean et al., 2018). Our current data therefore supports and reinforces previous works showing that social dominance is positively related to 5-HT neuronal activity (Kiser et al., 2012; Kim et al., 2015), and that while decreased levels of 5-HT promote social isolation (Higley et al., 1996), its increase promote social cooperation and contact (Paula et al. 2015; Anstey et al., 2009) and affiliative behaviors (Aan het Rot et al., 2006; Tse and Bond, 2002).

It is noticeable that aggressive behavior was not observed in any mouse that was socially isolated before the social task, independently of their hydratation condition (except one brief aggression from one dehydrated animal). This supports our previous work (Nosjean et al., 2015) showing that acute stress, but not temporary social isolation during adulthood, can trigger aggressive behavior in some mice. Social dominance is a normal behavior dissociated from aggressive behavior that we previously showed to be modulated by the cholinergic system activity (Nosjean et al., 2015) while aggressive behavior was modulated by the noradrenergic system activity (Cambon et al., 2010; Coura et al., 2013). However, other studies suggested causal links between increased aggression and low 5-HT activity (Audero, et al, 2013; Bjork et al., 1999; Caramaschi et al., 2007). One hypothesis to explain this discrepancy is that these authors consider extracellular 5-HT and its metabolite 5-HIAA (Dekeyne et al., 2000; Mir and Taylor, 1997; Sambunaris et al., 1997), whereas we look here at 5-HT neurons. We have recently shown that acute sleep restriction produced a decrease of 5-HT level in the prefrontal cortex, together with altered decision-making processes (Pittaras et al., 2018). It could therefore be of interest in future works to measure not only the cellular plasticity of 5-HT after dehydration but its consequences on 5-HT level and its metabolites in various brain areas. Besides, further study should clarify the signalling consequences of intracellular 5-HT increase after dehydration and its temporality, i.e., whether synthesis, degradation, reuptake and release of 5-HT are altered, by which mechanisms and which duration of dehydration is needed for them to take place. Conversely, it would be valuable to investigate other cognitive consequences of temporary dehydration. Nevertheless, to our knowledge, this is the first work showing neuronal plasticity of 5-HT in DRN and MRN after temporary dehydration stress and its detrimental effect on social interaction.

5-HT neurons had been found in higher density under dehydratation in *Gerbillus tarabuli* (Boukersi et al., 2018), a rodent adapted to dry environment. The fact that we showed a

similar plasticity of the serotonergic system in mice, rodents not particularly adapted to lack of water, suggests that this monoaminergic system may play a pivotal role in the rapid brain response to water homeostasis. This is in accordance with several reports providing evidence for involvement of this neurotransmitter in controlling vasopressin secretion (Popova et al., 2001), drinking behaviour (Reis et al., 1990), salt appetite (Cooper and Ciccocioppo, 1993), water intake and urine production (Olivares et al., 2003; Reis et al., 1994), supporting the view that serotonergic circuits originating from the mesencephalic raphe are implicated in hydromineral homeostasis (Fitzsimons, 1998; Franchini et al. 2002; McCann et al., 2003; Phillips et al., 1982; Reis et al. 1994).

In addition, it is well known that midbrain 5-HT neurons establish reciprocal interactions with thirst and water balance control areas, such as the subfornical organ (Tanaka et al., 2003), organum vasculosum laminae terminalis (Thrasher and Keil, 1987), and hypothalamo-pituitary axis (Maslova al., 1990; Popova et al., 2001). The latter is known to be markedly affected when animals are dehydrated (Langle et al., 2002) since it secretes vasopressin which controls water homeostasis in mammalians (Elgot et al. $2012_{a, b}$; Jones and Pickering, 1969). Furthermore, some areas involved in stress management and social behavior such as the prefrontal cortex (Abrams et al., 2004; Avale et al., 2011; Loiseau et al., 2008), the amygdala (Imai et al.,1986; Nosjean et al., 2018; Olsson and Phelps, 2007) and the hippocampus (McEwen et al., 2016; Kohler and Steinbusch, 1982) make important reciprocal anatomical connections with raphe nuclei (Groenewegen and Uylings, 2000; Hajós et al., 1998; Sesack et al., 1989), hence playing an important role in regulating executive function (Puig and Gulledge, 2011). Consequently, the wide distribution of 5-HT in the brain may make any change in its source (DRN and MRN) a potential cause of change in all functions controlled by areas innervated by 5-HT.

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