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► To cite this version:

Pascal Vaudin, Corinne Augé-Gouillou, Nathalie Just, Sakina Mhaouty-Kodja, Stéphane Mortaud, et al.. When pharmaceutical drugs become environmental pollutants: Potential neural effects and underlying mechanisms. *Environmental Research*, 2022, 205, pp.1-14. 10.1016/j.envres.2021.112495 . hal-03477405

HAL Id: hal-03477405

<https://hal.science/hal-03477405>

Submitted on 5 Jan 2024

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1 **Title : When pharmaceutical drugs become environmental pollutants: potential**
2 **neural effects and underlying mechanisms**

3

4 **Authors :** Pascal Vaudin^{1*}, Corinne Augé², Nathalie Just^{1#}, Sakina Mhaouty-Kodja³,
5 Stéphane Mortaud⁴ and Delphine Pillon¹.

6

7 ¹ Physiologie de la Reproduction et des Comportements, CNRS, IFCE, INRAE,
8 Université de Tours, PRC, F-37380, Nouzilly, France

9 ² UMR 1253, iBrain, University of Tours, INSERM, 37000 Tours, France.

10 ³ Sorbonne Université, CNRS, INSERM, Neuroscience Paris Seine – Institut de
11 Biologie Paris Seine, 75005 Paris, France.

12 ⁴ Immunologie et Neurogénétique Expérimentales et Moléculaires, UMR7355, CNRS,
13 Université d'Orléans, 45000 Orléans, France.

14 # Present address : Danish Research Center for Magnetic Resonance, Center for
15 Functional and Diagnostic Imaging and Research, Copenhagen University Hospital
16 Hvidovre, Hvidovre, Denmark.

17 * Corresponding author, e-mail address : pascal.vaudin@univ-tours.fr

18

19 **Keywords:** Pharmaceutical drugs, antibiotics, antidepressants, NSAIDs,
20 neurodevelopment, sexualization, environmental pollutants.

21

22 **Abstract:**

23

24 Pharmaceutical drugs have become consumer products, with a daily use for some of
25 them. The volume of production and consumption of drugs is such that they have
26 become environmental pollutants. Their transfer to wastewater through urine, feces or
27 rinsing in case of skin use, associated with partial elimination by wastewater treatment
28 plants generalize pollution in the hydrosphere, including drinking water, sediments,
29 soils, the food chain and plants. Here, we review the potential effects of environmental
30 exposure to three classes of pharmaceutical drugs, i.e. antibiotics, antidepressants
31 and non-steroidal anti-inflammatory drugs, on neurodevelopment. Experimental
32 studies analyzing their underlying modes of action including those related to endocrine
33 disruption, and molecular mechanisms including epigenetic modifications are
34 presented. In addition, the contribution of brain imaging to the assessment of adverse
35 effects of these three classes of pharmaceuticals is approached.

36

37

38 1. Introduction

39

40 Human and veterinary medicine uses a large variety of pharmaceutical drugs and their
41 consumption can reach several thousands of tons in some countries (Hider-Mlynarz et
42 al., 2018; Ortiz de García et al., 2013; Van Boeckel et al., 2014). The hepatic route
43 leads to their partial conjugation (glucuronidation, sulfation, methylation, for
44 elimination) leaving a proportion of pharmacologically active molecule in urine and/or
45 feces during their elimination (Kokki, 2010; Lucas, 2016; Rainsford, 2009; Verbeeck et
46 al., 1983). Pharmaceutically active compounds and their metabolites are not
47 completely eliminated by wastewater treatment plants transforming them into
48 environmental pollutants (Aemig et al., 2021; Bisognin et al., 2020; Chiffre et al., 2016;
49 Lonappan et al., 2016). At the worldwide level, pharmaceutical drugs are detectable in
50 surface and ground water with a transfer in sediment and soil showing a global
51 environmental contamination (Ahkola et al., 2017; aus der Beek et al., 2016; Awad et
52 al., 2014; Besse and Garric, 2008; Charuau et al., 2019; Desbiolles et al., 2018; Ortiz
53 de García et al., 2013; Wang et al., 2017).

54 In many species, brain development and function are dependent on internal factors
55 including steroid and thyroid hormones (Coumailleau et al., 2015; Duarte-Guterman
56 and Trudeau, 2010). In mammals, neurogenesis, cell migration and neuro-glial
57 differentiation in the cerebral cortex, hippocampus and hypothalamus are mediated
58 by sex steroids and thyroid hormones (Adhya et al., 2018; Parent et al., 2011; Zoeller
59 et al., 2002). During development, the sexual differentiation of the brain is regulated by
60 sex steroids through the masculinization of several brain areas including the preoptic
61 area (POA), a sexually dimorphic region of the hypothalamus regulating sexual
62 behavior in male and maternal behavior in female (Schwarz and McCarthy, 2008a). At
63 the adult stage, sex steroids play a crucial role in reproductive function since they
64 trigger the puberty and control the neuro-glial Gonadotropin-Releasing Hormone
65 (GnRH) and kisspeptin networks (Delemarre et al., 2008; Nestor et al., 2018; Vigil et
66 al., 2011). This dependence on steroids and thyroid hormones makes the brain a target
67 for molecules with endocrine disrupting activity during perinatal stage and adulthood.
68 In addition, thyroid hormones also target the brain through their involvement in
69 maturation phases. In particular, they have a crucial role for the myelination and myelin
70 turnover (Calzà et al., 2015). Moreover, recent studies show that thyroid hormones
71 play an important role in microglial development (Rousseau et al., 2020).

72 Many of the pharmaceutical drugs, which are now considered also as environmental
73 pollutants, exert their therapeutic action by interacting with the endocrine system and
74 for many of them, with neural cells.

75 The benefits of pharmaceutical drugs as therapeutic agents is no longer to
76 demonstrate. These molecules undergo both pre-clinical and clinical trial phases
77 before their marketing, consisting in toxicologic assessments to evaluate potential risks
78 (carcinogenicity, genotoxicity, reproductive toxicity...) according to the guidelines
79 proposed by the International Council on Harmonization or ICH (Goineau et al., 2013;
80 "<https://www.ich.org/>," n.d.) for human pharmaceuticals and VICH for veterinarian
81 compounds (<https://vichsec.org/en/>). The adverse impact of candidate drugs on the
82 central nervous system (CNS) are evaluated during the pre-clinical phase in
83 accordance with three guidelines: i) the guideline S7A (safety pharmacology studies)
84 with behavioral tests after a single injection of the pharmaceutical candidate in adult
85 animals, ii) the Pre- and Post-Natal development (PPND) study of the guideline S5
86 (R3) (reproductive toxicology) with behavioral tests after developmental exposure,
87 from E6 to PN21 in rat (from the 6th day of embryonic (E) development to the 21st Post-
88 Natal (PN) day) and iii) the guideline S11 or Juvenile Animal Study (JAS) for the
89 assessment of potential toxic effects on neonate, infant, child and/or adolescent with
90 behavioral tests, learning and memory tests and neuro-histopathology evaluations.
91 These regulatory assessments do not evaluate adverse effects of pharmaceutical
92 drugs at neuroanatomical, cellular or molecular level (Barrow, 2018;
93 "<https://www.ich.org/page/safety-guidelines>," n.d.). Only very few studies reported the
94 impact of these candidate molecules as environmental pollutants. Nevertheless, an
95 environmental risk assessment has to accompany an application for a marketing
96 authorization for a pharmaceutical. It consists in the determination of the Predicted
97 Environmental Concentration (PEC) of the drug substance in surface water and the
98 evaluation of adverse effects (if the PEC exceeds 0.01µg/L) on algae, Daphnia and
99 fish ([https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-
100 environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-risk-assessment-medicinal-products-human-use-first-version_en.pdf)).

101

102 The aim of this article is to review the potential adverse effects of three categories of
103 pharmaceutical environmental pollutants: the antibiotics, the antidepressants and the
104 anti-inflammatory drugs, on the development of the central nervous system (CNS) in
105 mammals. These three categories of pharmaceuticals were chosen according to the

106 following criteria: i) they are largely consumed, ii) they are quasi-systematically listed
107 in dosing studies reported in the scientific literature and iii) they are huge environmental
108 contaminants and notably for the hydrosphere. The mechanisms underlying the
109 potential endocrine disrupting effects of these pharmaceuticals will be discussed.
110 Since a delay exists between the exposition during development and the manifestation
111 of the adverse effects, at adult stage, we will expose the implication of epigenetic
112 modifications that may account for such delayed effects. Finally, we will briefly
113 introduce the potential of neuroimaging techniques for measuring and following the
114 endocrine changes induced by pharmaceutical agents.

115

116 **2. Neural effects of exposure to antibiotics**

117

118 Antibiotics are widely used in human medicine and most importantly in veterinary
119 medicine and agriculture (Jechalke et al., 2014; Machowska and Stålsby Lundborg,
120 2018). Therefore, their emission in the environment is mainly due to human sources
121 (hospital waste, and wastewater treatment plant...), and to a larger extent to
122 agricultural uses as therapeutic molecules but also as promoters of animal growth
123 (Puckowski et al., 2016). Previous research highlighted the worldwide presence of
124 antibiotics, with regional differences among the five analyzed regions across Eastern
125 and Western Europe, Asia, Africa and America (aus der Beek et al., 2016). Studies
126 monitoring the occurrence of pharmaceutical substances detected antibiotics in
127 wastewater treatment plants, surface water, groundwater sediments and aquatic
128 species including invertebrates and vertebrates (Ahkola et al., 2017; Awad et al., 2014;
129 Charuaud et al., 2019; Chiffre et al., 2016; Guo et al., 2021; Ortiz de García et al.,
130 2013; Wee et al., 2021; Xie et al., 2017). The resulting measured concentrations in the
131 environment vary from nanograms or micrograms to milligrams, with seasonal
132 variations and higher concentrations in winter than in summer (Awad et al., 2014; Kot-
133 Wasik et al., 2016).

134

135 In mammals, the neural effects of antibiotics were mainly studied in the context of
136 therapeutic use. Encephalopathy, optic neuropathy, seizures and peripheral
137 neuropathy are some examples of undesirable neurotoxic side effects associated with
138 their use (Koppel et al., 2001; Lamoth et al., 2009; Weinstein et al., 2009). It has been
139 shown, in particular, that following therapeutic use certain antibiotics induced

140 neurotoxic effects via the disruption of neurotransmitter release or the functional
141 alteration of neurotransmitter receptors, the increase in glutamate levels, the release
142 of cytokines in the brain as well as the modification of blood-brain barrier permeability
143 (Chow et al., 2005; Fiekers et al., 1983; Sugimoto et al., 2003).

144 Fetal, postnatal and early childhood are critical periods for neural development. The
145 disruption of the systems involved in brain homeostasis during these early periods of
146 neurodevelopment can have long-term consequences. Future studies are needed to
147 determine whether environmental exposure to antibiotics directly affects brain
148 development or whether microbiome molecules that travel to the brain disrupt gene
149 activity and cause cognitive deficits. In humans, a longitudinal cohort study showed
150 that 70% of European children who received antibiotics in early life, but not during
151 pregnancy, presented higher ratings of social difficulties, attention deficit hyperactivity
152 disorder and depression symptoms at a later age compared to non-exposed children
153 (Slykerman et al., 2017). It was shown in several mammalian studies that
154 administration of high doses of antibiotics during critical periods of development
155 induced long-term effects on brain and behavior by acting directly on the nervous
156 system or indirectly through microbiota modifications (reviewed by Champagne-
157 Jorgensen et al., 2019). In rodents, pre-breeding and/or gestational exposure to one
158 antibiotic (1% succinylsulfathiazole in diet) or to an antibiotic cocktail (5 mg/ml
159 neomycin, 5 mg/ml bacitracin and 1.25 µg/ml pimaricin in drinking water) elicited
160 changes in social and emotional behaviors (Degroote et al., 2016; Tochitani et al.,
161 2016). In agreement with this study, it was recently shown that perinatal exposure of
162 mice to a relatively low-dose of penicillin (31 mg/kg/d) induced long-term modifications
163 in the cortical cytokine expression, blood–brain barrier integrity, and behavior (Leclercq
164 et al., 2017). In particular, antibiotic-treated offspring exhibited impaired anxiety-like,
165 social and aggressive behaviors.

166 The cellular and molecular mechanisms reported for antibiotics are briefly summarized
167 here. Several scientific studies using electrophysiology have shown that some of these
168 antibiotics interfere with the glutamatergic and / or gabaergic systems. These
169 interactions had been demonstrated in the past for all quinolone antibiotics, such as
170 norfloxacin and ciprofloxacin, which inhibited the specific binding of ligands to GABAA
171 and ionotropic glutamate receptors in a concentration-dependent manner, with an IC20
172 of 220-930 µM and 70-480 µM, respectively, in mammalian cells (Dodd et al., 1989;
173 Halliwell et al., 1995). Given the importance of the gabaergic and glutamatergic

174 systems in various processes of neurogenesis, this raises the question of the risk of
175 chronic exposure to these antibiotics during development, due to environmental
176 contamination. Otherwise, the neurotoxic effects of some quinolones in combination
177 with certain non-steroidal anti-inflammatory drugs enhanced the inhibitory potency of
178 ciprofloxacin by approximately 3000-fold (100 μ M versus 0.03 μ M) as previously
179 reported (Halliwell et al., 1995).

180 Another cellular mechanism that was widely reported for the neural effects of antibiotics
181 involves microglia. It has been established for several years that certain antibiotics,
182 such as tetracyclines or minocycline, have an inhibitory action on microglial cells, the
183 immune cells of the central nervous system (Schmidtner et al., 2019; Scott et al., 2018;
184 Tikka et al., 2001). Recent studies demonstrated that microglial activation is not only a
185 hall-mark of neuroinflammation, but plays important roles during brain development.
186 Inhibition of microglial activation by minocycline was shown to induce extensive
187 neuronal cell death and impair neurogenesis in the subventricular zone (SVZ) and
188 synaptic pruning in the early postnatal and adolescent rodent brain, respectively (Inta
189 et al., 2016). These deleterious effects contrast with the neuroprotective actions of
190 minocycline at adult stages (Arnoux et al., 2014; Liu et al., 2017; Ueno et al., 2013).

191 It has been reported in mammals that catalase and glutathione s-transferase are also
192 modulated by tetracycline in some organs, including the brain (Satpute et al., 2017;
193 Turkan et al., 2020). It is of particular interest to note that these two enzymes are
194 important in microglial cells to promote pro-inflammatory astro-microglia
195 communication (Kano et al., 2019). Therefore, changes in microglial function could
196 trigger important brain disturbance if exposure to antibiotics occurs during
197 developmental periods.

198

199 Neural effects of exposure to antibiotics were also reported in aquatic models, which
200 with other wild life represent good sentinels for the environmental contamination
201 (*Animals as Sentinels of Environmental Health Hazards*, 1991). Exposure of zebrafish
202 to norfloxacin (600, 900 and 1200 mg/L) affected not only the hatching rate, increased
203 mortality and malformation rate of the embryos, but also inhibited the expression of
204 glial (*Glial fibrillary acidic protein* or *GFAP*), stem cell (*sex determining region Y-box 2*
205 or *sox2*) and mature neuronal (*enolase 2*) markers (Xi et al., 2019). In addition,
206 exposure to norfloxacin induced cell apoptosis in the brain of zebrafish embryos as
207 evidenced by measurement of caspase 3 activity and expression ratio of Bcl-2–

208 associated X (Bax) to B-cell lymphoma 2 (Bcl2). The apoptotic phenotype was rescued
209 by administration of MK-801, a noncompetitive antagonist of the N-Methyl-D-aspartate
210 (NMDA) receptor, suggesting that the activation of NMDA receptors mediated the
211 developmental neurotoxicity of this antibiotic. Another study focused on acute
212 exposure effects of tetracycline (5, 50 and 500 ng/L), an antibiotic subclass
213 representing the second highest frequency of detection in environmental matrices, in
214 the freshwater fish *Gambusi holbrooki* (Nunes et al., 2015). The results suggested the
215 existence of a cause-and-effect relationship between tetracycline exposure and
216 antioxidant effects, neurotoxicity, histological alterations and glutathion-S-transferase,
217 catalase and acetylcholinesterase enzymatic activities as described above in
218 mammals.

219 The potential effects of antibiotics were also studied in the context of combined
220 exposure with other environmentally detected pharmaceuticals. Liu et al. (2017)
221 showed that combined exposure of *Crucian carp* to an antibiotic, erythromycin, at 2
222 µg/L and an anti-fungal molecule, ketoconazole, at 0.2, 2 or 20 µg/L inhibited
223 acetylcholine esterase activity and swimming behavior and enhanced shoaling.
224 Exposure of fish, *Astyanax bimaculatus*, to sewage effluents added with five
225 pharmaceuticals including four antibiotics (ciprofloxacin at 11.44 µg/L, oxytetracycline
226 at 7.93 µg/L, sulfamethoxazole at 188.69 µg/L, trimethoprim at 30.65 µg/L) and
227 paracetamol at 151.17 µg/L increased glutathione-S-transferase activity in the brain
228 (Bisognin et al., 2020).

229

230 Whether antibiotics found in the environment trigger neural adverse effects for human
231 health and environment through endocrine mode(s) of action still needs a thorough
232 investigation, in particular at environmental doses. However, some evidences in
233 aquatic animals point out a possible alteration of neuroendocrine systems. Chronic
234 exposure of Japanese medaka (*Oryzias latipes*) for 120 days to cefadroxil at 84.8 µg/L
235 and cefradine since 73.9 µg/L impaired growth and reproduction (Kim et al., 2017).
236 These effects were associated with altered expression levels of *gnrh1*, *gnrh2*, estrogen
237 receptors (*esr1*, *esr2*), and *cyp19b* in the brain (Kim et al., 2017). Modifications in the
238 pituitary expression of *gnrh1r* and *gnrh2r* encoding GnRH receptors and in estradiol
239 levels were also observed (Kim et al., 2017). In a previous study, the same group
240 showed that chronic exposure of Japanese medaka to lincomycin at 0.42 mg/L
241 significantly reduced juvenile survival at 30 day post-hatch (Kim et al., 2012).

242 Interestingly, exposure to lincomycin also increased vitellogenin levels in male fish at
243 90-day post-hatch. In the same study, exposure of human adrenal cells to lincomycin
244 also altered steroidogenesis and increased estradiol concentrations. In accordance
245 with these data, another antibiotic, ciprofloxacin has been previously reported to inhibit
246 the activity of cytochrome P450, a key enzyme in hormone synthesis, in rat and human
247 (Granfors et al., 2004; McLellan et al., 1996). Besides these studies reporting
248 alterations in the gonadotropic axis and/or in steroidogenesis, thyroid disruption was
249 also observed in a study addressing long-term exposure of Zebrafish embryos to
250 environmentally relevant concentrations of oxytetracycline (1000 or 5000 ng/L) from 2
251 h to 120 d post-fertilization (Yu et al., 2020). In particular, exposure to oxytetracycline
252 increased triiodothyronin concentrations, reduced levels of thyroid stimulating
253 hormone, and affected growth and development of Zebrafish. From these studies, it
254 appears that relatively low doses of antibiotics can exhibit endocrine modes of action
255 in aquatic models, through impairment of the gonadotropic or the thyroid axes. This
256 raises the question of the potential adverse effect on the nervous system, given the
257 importance of thyroid and sex hormones in neural processes during critical periods of
258 development.

259

260 **3. Effects of antidepressants on CNS development**

261

262 Numerous psychiatric pharmaceuticals are widely prescribed to treat mental illnesses
263 such as depression, psychosis, anxiety, epilepsy or mood disorders. Therefore antide-
264 pressants constitute one of the most commonly prescribed drugs in developed coun-
265 tries (France, Aemig et al., 2021; Spain, Ortiz de García et al., 2013; USA, Pratt et al.,
266 2017; reviewed by Castillo-Zacarías et al., 2021). The growing consumption of antide-
267 pressants is associated to a growing occurrence of these drugs in urban waters as well
268 as in rivers and oceans (aus der Beek et al., 2016; Martin et al., 2019; Mole and Brooks,
269 2019; Saaristo et al., 2019), leading to an emerging environmental contamination by
270 antidepressants. Antidepressants act directly on brain's biochemistry by modifying
271 neurotransmitter metabolism. Various classes of antidepressants implicate different
272 mechanisms of action within the CNS, regulating notably the serotonin neurotrophic
273 effects. Each class is identified according to its mechanism of action on neurotransmit-
274 ters: the selective serotonin reuptake inhibitors (SSRIs), which are the most widely

275 prescribed (Kulikov et al., 2018); the serotonin and norepinephrine reuptake inhibitors
276 (SNRIs); the serotonin modulators and stimulators (SMSs); the serotonin antagonists
277 and reuptake inhibitors (SARIs); the noradrenergic and selective serotonergic anti-
278 depressants (NaSSAs); the norepinephrine reuptake inhibitors (NeRIs); the serotonin,
279 norepinephrine and dopamine reuptake inhibitors (SNDRI) or triple reuptake inhibitors
280 (TRIs); and the melatonin and serotonin agonists (MaSAs) (Fitzgerald and Watson,
281 2019). SSRIs are mainly prescribed for treating major depressive disorder, and partic-
282 ularly perinatal depression (Latendresse et al., 2017). Among them, fluoxetine (Pro-
283 zac®) is metabolized by cytochrome P-450 isoenzymes to norfluoxetine, which retain
284 the pharmacological activity (Mandrioli et al., 2006). This active metabolite is elimi-
285 nated in the urine and then disseminates into wastewaters. Fluoxetine and norfluoxe-
286 tine are widely detected into various environmental compartments such as surface,
287 ground, marine and drinking waters, soils and sediments in the range of ng/L to mg/L
288 (Biel-Maeso et al., 2018). In the United Kingdom, fluoxetine can be detected in drinking
289 water at low concentrations (0.27 ng/L; Peng et al., 2019). In this review, fluoxetine is
290 taken as an example of SSRIs antidepressant that constitutes an environmental pollu-
291 tant.

292 According to a report from the Organization for Economic Cooperation and
293 Development (OECD) on pharmaceuticals consumption in 2019 (OECD iLibrary), the
294 consumption of antidepressant drugs doubled in OECD countries between 2000 and
295 2017. Such an increase in human consumption generated an amplification in
296 environmental contamination (reviewed by Castillo-Zacarias et al., 2021). Therefore
297 antidepressants constitute emerging environmental pollutants. Regarding the wide
298 dissemination of antidepressants in the environment, numerous studies demonstrated
299 deleterious biological effects on aquatic wildlife ecosystems due to antidepressant
300 contamination in the environment (reviewed by Sehonova et al., 2018). Antidepressant
301 dissemination in rivers, estuaries and coastal waters exposes aquatic organisms like
302 fishes, amphibians or mollusks, leading to alterations in essential physiological and
303 behavioral processes through neurological and neuroendocrine effects. For example,
304 in eastern mosquitofish (*Gambusia holbrooki*), fluoxetine exposure at environmental
305 doses alters antipredator and anxiety-related behaviors (Martin et al., 2019, 2017), as
306 well as reproductive behaviors such as courtship and sexual partners interactions
307 (Martin et al., 2019) or copulatory behavior (Bertram et al., 2018; Fursdon et al., 2019).

308 In the meagre (*Argyrosomus regius*), Duarte et al. (2020) demonstrated alterations in
309 fish growth, oxidative stress, detoxification mechanisms and lipid peroxidation in the
310 liver (Duarte et al., 2020). Such results suggest an endocrine disruption mode of action
311 implicating alterations within the hypothalamic-pituitary-adrenal (HPA) axis, the
312 gonadotropic axis or the thyroid hormones regulation.

313 Beyond such effects disturbing aquatic wildlife ecosystems, antidepressant
314 metabolites concentrate in brain and liver tissues (David et al., 2018; Pan et al., 2018),
315 as well as in plasma, of fishes consumed by humans (Sims et al., 2020). Therefore,
316 either through direct effects via drinking water or through indirect effects via aquatic
317 food, environmental contamination by antidepressants may constitute a risk for human
318 health.

319 Antidepressant drugs such as fluoxetine are commonly prescribed in women for
320 treating major depressive disorder during pregnancy and/or postpartum depression.
321 As these drugs cross the placental barrier (Arumugasaamy et al., 2019; Hendrick et
322 al., 2003) and diffuse in breast milk (Schoretsanitis et al., 2020, 2019), and because of
323 their action on neurotransmitter metabolism, antidepressants are expected to affect
324 the developing fetal and postnatal brain of respectively fetuses and newborns. Then
325 antidepressants may constitute a risk for human health as their potential disrupting
326 effects during embryonic and postnatal brain development may alter development,
327 growth and regulation of neural systems, as well as neural plasticity, with long-term
328 consequences.

329

330 In rodents, developmental exposure to antidepressants during prenatal life and/or
331 lactation has been demonstrated to induce long-term endocrine, behavioral and neural
332 alterations. Most of the results are relatives to the control of the HPA axis. In mice,
333 developmental fluoxetine exposure alters endocrine and behavioral response to stress
334 in adult female and male progeny (Avitsur, 2017; Avitsur et al., 2016). Indeed prenatal
335 fluoxetine exposure disrupts the negative feedback control of the HPA axis response
336 to stress and reduces anxiety- and depressive-like behaviors at adulthood, that could
337 be due to a glucocorticoid insensitivity. In rats, postnatal fluoxetine exposure up to
338 weaning induces in male offspring only, at adult stage, an increase in anxiety-like
339 behavior and impairments in HPA axis negative feedback (Gobinath et al., 2016).
340 These impairments are associated with sexually dimorphic adult hippocampal
341 neurogenesis alterations, since hippocampal neurogenesis is amplified in adult males

342 after preweaning fluoxetine exposure and reduced in adult females. Otherwise,
343 perinatal fluoxetine has been shown, in male rats, to decrease corticosterone levels,
344 to increase both serotonin levels in the hippocampus and pre-synaptic density in the
345 dentate gyrus (Gemmel et al., 2017), and to induce sexually differentiated effects on
346 hippocampal neurogenesis and glucocorticoid receptor density (Gemmel et al., 2019).
347 Moreover, on prenatally stressed progeny, developmental fluoxetine exposure
348 modifies the dopaminergic system in the hippocampus and decreases monoamine
349 levels (Gemmel et al., 2016). Decreases in hippocampal BDNF IV and its receptor TrkB
350 mRNA expression after developmental fluoxetine exposure constitute other molecular
351 processes that may be implicated in long-term programming effects on brain and
352 behavior (Boulle et al., 2016).

353 Other studies reported fluoxetine-induced alterations within the reproductive function.
354 In male mice, fluoxetine exposure during fetal development and lactation reduces at
355 adulthood sexual motivation (Gouvêa et al., 2008). In rats, developmental fluoxetine
356 exposure induces in adult male sexual behavior impairments (Rayen et al., 2013).
357 Moreover, it decreases the area of the sexually dimorphic nucleus of the preoptic area
358 (SDN-POA), implicated in rodents in the control of sexual behavior.

359 Comparable to fluoxetine, sertraline, a frequently prescribed SSRI, has been
360 demonstrated to modify as well neuroendocrine and behavioral parameters in progeny
361 of maternal exposure in rodents. In rats, Kott et al. (2019) described alterations in HPA
362 axis secretions, anxiety behavior and cognition, with sex-specific effects in the adult
363 offspring (Kott et al., 2019). Moreover, sertraline developmental exposure throughout
364 gestation modifies permanently in adult mice the levels of serotonin receptors and
365 transporters mRNAs in the cerebral cortex (Meyer et al., 2018).

366 Altogether, these results demonstrate long-term endocrine and behavioral, as well as
367 neural, effects after prenatal and perinatal SSRIs exposure. The neural effects are
368 suspected to be involved in endocrine and behavioral alterations, as some remodeling
369 of neural circuits in early life are able to modulate behavioral responses at adulthood.
370 If literature reporting endocrine, behavioral and neural effects induced by
371 developmental exposure to pharmacological SSRI doses is significant, in contrast
372 literature related to human risk constituted by antidepressants exposure at
373 environmental doses during pre- and peri-natal development is poorly documented.
374 We can notice that, through *in vitro* and *in silico* approaches using differentiated human
375 neuroblastoma cells treated with a mixture of psychoactive pharmaceuticals including

376 fluoxetine at environmentally relevant concentrations, Kaushik et al. (2016, 2017)
377 identified alterations in neuronal gene expression associated with neurological
378 disorders such as Autism Spectrum Disorders (ASD), Alzheimer's disease and
379 schizophrenia. Among the genes exhibiting expression alterations, several genes
380 coding synaptic proteins associated with ASD are affected (Kaushik et al., 2017, 2016).
381 Finally, it can be mentioned that some indirect effects may be suspected, implicating
382 the gut microbiota. Gut microbial metabolites participate to homeostasis and
383 development. If maternal SSRIs treatment modifies maternal microbiota, the progeny
384 central nervous system may be the trigger of alterations with long-term consequences
385 (Ramsteijn et al., 2020).

386 Therefore more studies using environmentally relevant doses are needed to evaluate
387 the risk for human health of antidepressants environmental contamination.
388 Technological progress is aiming to remove pharmaceuticals from sewage (reviewed
389 by de Oliveira et al., 2020). If, over last years, such progress has improved, however,
390 such as for most of pharmaceuticals, wastewater treatments remain only partially
391 efficient in removing antidepressant molecules. Considering the diversity of
392 pharmaceuticals detected in various environmental compartments, notably
393 antidepressant molecules, triggering the CNS and neurotransmitter metabolism,
394 cocktail effects have to be defined.

395

396 **4. NSAIDs and neurodevelopment**

397

398 Nonsteroidal anti-inflammatory drugs (NSAIDs) are pharmaceuticals that reduce pain,
399 decrease fever and inflammation. Diclofenac, ibuprofen, indomethacin, ketoprofen,
400 naproxen and paracetamol (or acetaminophen) are the most common, they are free
401 sold in numerous countries (Rayen et al., 2013). In 2010's approximately 250 000 kg
402 of ibuprofen were consumed in Germany, France, Spain; 1 065 000 kg and 3 300 000
403 kg of paracetamol were consumed respectively in Spain and France (Chiffre et al.,
404 2016; Ortiz de García et al., 2013). Pharmacokinetic studies show that NSAIDs are
405 excreted *via* urine and feces in conjugated and free forms (Lucas, 2016; Rainsford,
406 2009; Small, 1989). These metabolized and non-metabolized NSAIDs forms in addition
407 to creams, gel and patch are not totally eliminated by wastewater treatment plants
408 (Wang et al., 2017). Therefore, NSAIDs are frequently dosed in the hydrosphere,
409 sediments and soil showing a general contamination (Amalric and Togola, 2011; aus

410 der Beek et al., 2016; Ortiz de García et al., 2013). The consequences of this general
411 pollution is the contamination of the animal trophic chain, from phytoplankton to
412 predators (Bean et al., 2018; Xie et al., 2017), vegetables (Wu et al., 2013) and drinking
413 water. Indeed, contamination of drinking water is reported in several studies in multiple
414 areas with maximum concentrations of 1 350 ng/L for ibuprofen in United States, 166
415 ng/L for ketoprofen and 114 ng/L for diclofenac in Poland and 210 ng/L for paracetamol
416 in France (Caban et al., 2015; Kot-Wasik et al., 2016; Mompelat et al., 2009; Togola
417 and Budzinski, 2008). This generalized environmental contamination, outside the
418 therapeutic context, leads to chronic human exposure to NSAIDs which physiological
419 effects need to be documented.

420

421 NSAIDs exert their pharmaceutical action by inhibiting the activity of cyclooxygenases
422 COX-1 and COX-2 enzymes (Brideau et al., 1996; Patrignani et al., 1997; Van Hecken
423 et al., 2000). COX-1 and COX-2 are encoded by *PTGS1* and *PTGS2* (*prostaglandin-*
424 *endoperoxide synthase*) genes respectively and catalyze the bis-dioxygenation and
425 reduction of Arachidonic Acid to Prostaglandin E2 (PGE2), mediator of neuropathic
426 pain (Ma and Quirion, 2008; Rouzer and Marnett, 2009). For the CNS pain, NSAIDs
427 are largely prescribed or indicated in case of headache or migraine in adult and their
428 toxicity were reported in case of overdose (Auriel et al., 2014; Becker, 2015; May,
429 2018). If adverse effects of NSAIDs are well identified in adult and if the communication
430 exists to sensitize the consumers and to prevent CNS disorders, little is known about
431 the effects of NSAIDs exposure during brain development. However, developmental
432 exposure to NSAIDs exists as shown by several studies. First, placenta is not a barrier
433 preventing NSAIDs fetal exposure since Siu (2000) demonstrated that after an
434 administration of diclofenac to pregnant women before legal termination of pregnancy,
435 this drug was measured in amniotic and coelomic fluids with a mean ratio of 0.95 for
436 maternal plasma/fetal tissues. Fetal exposure was confirmed with the presence of
437 ibuprofen, naproxen and indomethacin in the meconium of 101 infants in the Michigan
438 (Alano et al., 2001). NSAIDs exposure is potentially prolonged to neonatal stage since
439 ibuprofen and naproxen were measured in human breast milk at 0.37 µg/kg and 1.9
440 µg/kg respectively. In the same study, diclofenac was dosed at 0.09 µg/kg, ketoprofen
441 at 0.15 µg/kg and naproxen at 0.35 µg/kg in powdered infant milk according the
442 provenance (Azzouz et al., 2011). Knowing that NSAIDs inhibit the production of

443 PGE2, we can ask ourselves if developmental exposure to NSAIDs has an impact on
444 the brain differentiation.

445

446 PGE2 is involved in the development of specific brain areas and in particular in
447 hypothalamus and cerebellum differentiation. Its four receptors, EP1 to EP4 (or
448 PTGER1-4: prostaglandin E receptor) are not ubiquitously distributed in the CNS. In
449 rat, maximum expression of *EP1* is found in pituitary gland and cerebellum, in
450 hypothalamus and pituitary gland for *EP2*, in thalamus and hypothalamus for *EP3* and
451 cerebellum and cortex for *EP4* (Myren et al., 2012). Several studies showed a direct
452 implication of PGE2 in the development of the cerebellum and the preoptic area (POA),
453 a subdivision of the hypothalamus controlling masculinization of adult sex behavior
454 (Schwarz and McCarthy, 2008b). Amateau and McCarthy (2002) show, using POA
455 neurons of newborn female rats (1-2 h), that PGE2 changes neuron morphology by
456 increasing the number and density of dendritic spines. Using *in vivo* experiments, they
457 reported the expression of PGE2 receptors *EP1*, *EP2* and *EP3* genes in the POA of
458 PN0 female rat. In the same study, it was demonstrated that PGE2 is a mediator of E2
459 signal for the induction of the Spinophilin protein production, a marker of dendritic
460 spines. Finally, Amateau and McCarthy (2002) have also identified the POA as a
461 sexual dimorphic structure since they observed a greater Spinophilin protein quantity
462 (two and half more) in newborn males than in newborn females (Amateau and
463 McCarthy, 2002). Two years later, the same team has demonstrated that PGE2 is
464 directly implicated in the male sexualization of the developing POA and induced sex
465 behavior in adult male rat. They also showed that E2 regulates the synthesis of PGE2
466 by upregulating *PTGS2* expression and COX-2 enzyme production in the POA of 3
467 days old rat (Amateau and McCarthy, 2004). The cerebellum is an area located in the
468 rostral roof of the 4th ventricle and functionally associated with emotional control, motor,
469 cognitive, and social behaviors (Adamaszek et al., 2017; Voogd and Glickstein, 1998).
470 In 2012, Dean et al. brought the demonstration for the pivotal role of PGE2 in the
471 development and functional acquisition of the cerebellum. In this study it was reported
472 that PGE2 regulates the dendritic spines of Purkinje cells and cerebellum volume
473 between PN7 and PN13 in male and female rats. This involvement of PGE2 in the
474 differentiation of the cerebellum in this short window is directly associated with adult
475 behavior induction like play, sensory threshold and object exploration (Dean et al.,
476 2012). These studies indisputably show a key role of PGE2 in the differentiation of

477 POA and of the cerebellum and therefore of the brain at an early postnatal stage.
478 NSAID-inhibition of PGE2 during brain development could have disruptive effects and
479 could be a real concern.

480

481 Very few studies were published on the toxicological effects of NSAIDs at
482 environmental doses. Exposing common carps with NSAIDs-manufacturing plant
483 effluent causes genotoxicity and apoptosis in blood cells (SanJuan-Reyes et al., 2015).
484 Other studies show, after environmental NSAIDS exposure, an induction of oxidative
485 stress in fish, crustaceans and bivalves (Gonzalez-Rey and Bebianno, 2014; Novoa-
486 Luna et al., 2016; SanJuan-Reyes et al., 2015). Teratogenicity experiments using
487 *Xenopus* embryos indicate that diclofenac at environmental doses causes
488 malformation of several organs with acephaly, cephalic edema and a diminution of
489 axial length (Chae et al., 2015). No studies reporting NSAIDs effects on neurotoxicity
490 in mammals are available, nevertheless inhibiting COX-1 and COX-2 enzymes and so
491 preventing PGE2 production has a negative impact on brain development. *In vitro*
492 incubation of POA neurons with indomethacin prevents dendritic spines formation and
493 spinophilin production induced by PGE2 (Amateau and McCarthy, 2002).
494 Administration of indomethacin in newborn rats (6hrs of birth) blocks the production of
495 spinophilin and decreases the density of dendritic spines in POA male rats (Amateau
496 and McCarthy, 2004, 2002). This structural modification of POA impacts the behaviors
497 it controls. Indeed, exposure of neonate rats (between PN0 and PN1) to NSAID
498 disturbs sexual behavior in adult males, not in adult females. Thereby a neonatal
499 indomethacin treatment induces an decrease of sexual adult male behavior with an
500 increasing of latency to mount, intromission, a decreasing of mounts and intromissions
501 frequency and a cancellation of ejaculation (Amateau and McCarthy, 2004). Non-
502 neuronal cells of the POA are also sensitive to NSAIDs since POA microglial cells are
503 more numerous and ameboid in male than female in neonate rats. This sexual
504 dimorphism, dependent of PGE2, is abolished with indomethacin treatment inducing a
505 loss of masculinization of the POA (Lenz et al., 2013). Curiously the inhibition of COX-
506 1 and COX-2 enzymes in the cerebellum has an opposite effect on neuron morphology
507 but still impacts adult behavior. Treating neonate rats with NSAIDs (indomethacin and
508 paracetamol) between PN7 and PN13 induces an increase of dendritic spine length of
509 Purkinje cells only in male PN14 cerebellum and a modification of behaviors associated
510 to this cerebral structure. Male adult rats exposed to NSAIDs in neonatal stage present

511 a reduction of play behavior and the sensory threshold and an increase of object
512 exploration time (Dean et al., 2012). NSAIDs doses used in these studies are
513 pharmaceutical and greatly extra-environmental, but a chronic NSAID developmental
514 exposure with environmental doses and especially in the precocious postnatal window
515 could have a real impact and remains largely underexplored.

516

517 **5. When drugs become environmental pollutants: what about epigenetics** 518 **consequences?**

519

520 Recently, it became evident that epigenetics prior to or around the birth can profoundly
521 modify brain development and can be linked to various neurodevelopmental
522 syndromes (reviewed by Lo and Zhou, 2014). Epigenetics disorders fit well with the
523 time lag often observed for such syndromes, which may appear many years after
524 exposure or in offspring. Although less is known about epigenetic consequences of *in*
525 *utero* and perinatal chronic exposures to environmental pollutants, data presented in
526 the current review ask questions about the putative role of epigenetics input, especially
527 in behavioral changes observed between childhood and adulthood, or for the brain
528 sexualization. For instance, in human, maternal exposure to environmental heavy
529 metals during pregnancy is associated with differential DNA methylation in new-borns,
530 especially on genes involved in neurogenesis (Zeng et al., 2019).

531

532 This question is made relevant by the outcome of works establishing a causal link
533 between a well-known endocrine disrupting compound, the Bisphenol A (BPA), and its
534 epigenetic consequences. In mouse, BPA exposure modifies the expression of several
535 genes involved in brain development by altering the genomic imprinting at various
536 genetic loci. This effect is transmitted across generations. In addition, BPA has been
537 suggested to affect the DNA methylation status, as well as histones post-translational
538 modifications after *in utero* exposure (reviewed by Santoro et al., 2019). Similar effects
539 are suspected about other pollutants, such as Permethrin (Bordoni et al., 2019), for
540 which low dosage exposures during neonatal brain development led to significant
541 reduction of H3K9me3 marks at Th and Nurr1 promoter regions, both genes being
542 related to the dopamine-synthesis pathway. Although these pollutants are outside the
543 scope of our review, they clearly illustrate the potential epigenetic impact of pollutants.
544 What's about drugs when they are pollutants? Even if no studies are available at this

545 level (epigenetics aftermath of drugs detected in the environment), data are now known
546 on the epigenetic effect of drugs when administered during pregnancy or gestation, or
547 around the perinatal period.

548

549 Antibiotics.

550 In addition to the overall effects of antibiotics on the nervous system (described above),
551 various studies concerning the epigenetics alterations mediated by antibiotics have
552 been published. It was demonstrated that zebrafishes are sensitive to a common
553 biocide (Triclosan), when administrated to 8-cells developing larvae at low doses (50
554 or 100 µg/L), until hatching. This treatment modifies DNA methylation in a locus-
555 specific manner (mainly within introns and intergenic sequences), while global DNA
556 methylation is not affected. Consequently, the expression of few genes is modified.
557 Interestingly, in zebrafish, antibiotics trigger mechanisms of acclimation leading to an
558 increase resistance of organisms. Here, DNA methylations are likely to precede the
559 adaptive response (Falisse et al., 2018).

560 Recently, a special attention was paid to how the composition of gut microbiota may
561 contribute to establish epigenetic changes, leading to modulation of lifelong health and
562 diseases, *via* the gut-brain axis. In humans, the role of maternal and neonatal nutrition,
563 as well as microbiota composition has been reviewed by Indrio et al (2017). The period
564 during which epigenetic imprinting is the most active is referred as the 1,000 days
565 period (from conception to the second anniversary). During this period the microbial
566 colonization takes place first *in utero*, then after birth. Because the microbiota-related
567 epigenetic regulation of gene expression could take place in various brain regions, the
568 impact of the “quality” of the maternal microbiota has been suspected of importance in
569 preventing or promoting brain development disorders (Indrio et al., 2017). Evidence
570 accumulate that a disturbed microbiota is related to various neurodegenerative
571 diseases (Quigley, 2017). In fact, gut microbiota is now looked as an important
572 epigenetic regulator since some of their metabolites (as SCFAs) act as HDAC
573 inhibitors, and play a role through DNA methylation, post-transcriptional histone
574 modification, and chromatin restructuring, all together resulting in altering genes
575 expression (Kaur et al., 2021). By the way, pharmacological factors (such antibiotics)
576 that modify microbiota can be related to the development of chronic diseases. In
577 human, the predominant gut microbiota of pregnant women was associated to the
578 postpartum methylation profile of their blood DNA and correlated with differential

579 methylation status of gene promoters linked to cardiovascular diseases (Kumar et al.,
580 2014).

581 Even if there is no direct evidence between epigenetics, antibiotics in the environment
582 and neurodegenerative diseases, all the ingredients are there to consider a possible
583 impact, including *via* pathways other than the microbiota.

584

585 Antidepressants.

586 Literature related to human risk constituted by antidepressants exposure at
587 environmental doses during pre- and peri-natal development is poorly documented,
588 but epigenetic consequences of maternal treatment during pre- and perinatal
589 development are more documented (in animal models or in human clinical studies).
590 Since fluoxetine is commonly prescribed for the treatment of depression in pregnancy,
591 its impacts on *in utero* exposed children has been questioned, including at the
592 epigenetics level. Alteration of DNA methylation levels has been detected in the
593 hippocampus of rats that were exposed to fluoxetine during their development (Silva
594 et al., 2018). This alteration correlates with modifications of the anxiety-related (social)
595 behavior at adulthood, as result of an acquired imprinting. These studies converged
596 with the findings of Boulle et al. (2016), which demonstrate that fluoxetine modifies the
597 epigenetic regulation of the hippocampal brain-derived neurotrophic factor (BDNF)
598 coding gene, in the offspring of treated female. It was actually found that
599 developmentally administered fluoxetine increases H3K27me3 levels at the BDNF
600 promoter, in accordance with the decreased expression of BDNF mRNA in the
601 hippocampus of offspring. More, these modifications were associated to increased
602 depressive-related behaviors in adult female offspring, suggesting a long-term effect
603 of fluoxetine treatment during gestation and/or lactation. Epigenetic effects of
604 developmental exposure to fluoxetine were also suggested by studies on zebrafish
605 (Boulle et al., 2016). In addition, a 6-day exposure to fluoxetine at a fetus-relevant
606 concentration inhibits cortisol secretion at adulthood in developmentally exposed
607 zebrafish, and this alteration is persistent for three generations of unexposed progeny,
608 as well as alterations in exploratory behaviors in males (Vera-Chang et al., 2018).
609 Transcriptomic analysis of kidneys cells showed that fluoxetine exposure modified
610 signaling pathways implicated in cortisol production on animals of the three
611 generations. Neural effects are suspected to be involved through the HPA axis control
612 (Vera-Chang et al., 2018).

613 In human, the involvement of epigenetic mis-regulations is suggested through *in vitro*
614 and *in silico* approaches using differentiated human neuroblastoma cells treated with
615 a mixture of psychoactive pharmaceuticals including fluoxetine at environmentally
616 relevant concentrations. A recent study identified alterations in neuronal gene sets
617 expression associated with neurological disorders such as Autism Spectrum Disorders
618 (ASD), Alzheimer's disease and schizophrenia. Among the genes exhibiting
619 expression alterations, several genes coding synaptic proteins associated with ASD
620 were affected (Kaushik et al., 2017).

621

622 *Non-Steroid Anti-Inflammatory Drugs (NSAIDS).*

623 Here again, no studies are available to prove a direct correlation between NSAIDS (as
624 pollutants) and epigenetics alteration of brain development. But there is straight
625 evidence of (i) epigenetic changes due to NSAIDS, (ii) the epigenetic control of brain
626 feminization and (iii) the epigenetic control of PGE2 biosynthesis *via* an induced COX2
627 expression. In this context, it is tempting to propose that chronic exposure to NSAIDS
628 may alter sexual behavior also through epigenetic mechanisms.

629 Epigenetic changes due to NSAIDS have been studied in patients having various
630 cancers. Clinical trials and *ex-vivo* analyses both suggest that aspirin and other
631 NSAIDS induced changes in promoters' methylation, thus leading to gene silencing.
632 This effect has been attributed to DNMT1 inhibition (reviewed by Yiannakopoulou,
633 2014). In animal studies, this local effect was found associated to an overall effect.
634 Indeed, NSAIDS reverse global DNA hypomethylation in colon cancer rat-models.
635 Finally, the fact that aspirin is known to acetylate proteins leads to assay whether it
636 also acetylates histones, among other cellular proteins. This is actually the case, but it
637 remains to establish whether this direct post-translational modification impairs gene
638 expression (Bhat, 2011). More recently, it has been found that Ibuprofen and
639 Ibuprofen-CoA causes dose-dependent inhibition of histone acetylation, especially
640 H2B K12/K15Ac and H3 K56Ac, in cultured cells (Shrimp et al., 2018).

641 Because epigenetics is involved in various endogenous and exogenous pathways to
642 exert long-term control over gene expression, it was tempting to verify its role in
643 estradiol-mediated brain masculinization, an effect herein described (see previous
644 paragraph). Doing so, it was demonstrated that estradiol suppresses DNMT activity,
645 leading to an overall DNA demethylation in male developing POA. This study confirms

646 that feminization is an active repression of masculinization process, reinforced by
647 epigenetics imprints (Nugent et al., 2015).

648 Finally, the epigenetic activation of the COX2 promoter by p300, a histone acetyl
649 transferase, has been confirmed in activated monocytes, leading to PGE2 production
650 (Liu et al., 2020). As mentioned before, increased COX2 expression and PGE2
651 production within dendritic spines leads to the hypothesis that COX2 is an active
652 modulator of neuronal plasticity, involved in sex differentiation (Amateau and
653 McCarthy, 2002). The fact that COX2 activation appears finely and strictly controlled
654 at the spatial level speaks up for an epigenetic control in neurons, as previously
655 demonstrated in monocytes.

656

657 In conclusion, albeit no direct evidence about epigenetic consequences of *in utero*
658 and/or perinatal chronic exposures to drugs as environmental pollutants still exists,
659 converging evidence suggests a possible impact. It therefore appears important not to
660 overlook epigenetics effects when addressing this issue. Further studies remain to be
661 done, especially in humans. The central issue being the dose at which these effects
662 could be significant.

663

664 **6. Non-invasive neuroimaging to advance knowledge on EDCs?**

665

666 Evidence from epidemiological and experimental data of the close relationship
667 between environmental contaminants and adverse functional and metabolic effects are
668 mounting. Nevertheless, to date, there are very few dedicated non-invasive and
669 translational methods with the ability to measure, demonstrate and validate a direct
670 and specific link between the alteration of the function of the endocrine system and
671 Endocrine disruptor compounds (EDCs) *in-vivo* in the brain. Methodologies and
672 models are lacking for evaluating the mechanisms and pathways underlying the effects
673 of EDCs and their development into diseases. Here, the potential of magnetic
674 resonance (MR) techniques to assess risk factors induced by potential EDCs is
675 introduced. In this paragraph, we aim to show in a non-exhaustive manner that non-
676 invasive neuroimaging methods can be adapted to further advance and fasten
677 knowledge on EDCs.

678

679 Magnetic Resonance Imaging and Spectroscopy (MRI and MRS) (Haacke et al.,
680 1999).

681 That Nuclear Magnetic Resonance (NMR) techniques are powerful for the investigation
682 of the structure, function and metabolism of the brain both in animal models and human
683 is not to demonstrate anymore. MR imaging (MRI) is well known for its non-
684 invasiveness, its important contrast between soft tissues and its high spatial resolution
685 compared to other macro-imaging techniques (X rays, Positron Emission Tomography,
686 Ultrasound). In addition, crucial technological developments have been carried out
687 during the past 20 years and the advent of high magnetic field strength horizontal
688 superconducting magnets (up to 11.7T in humans, up to 21T in rodents) coupled to
689 improved hardware enabled an unprecedented increase of the sensitivity (Hespel and
690 Cole, 2018; Wald, 2019), the spatial and temporal resolutions and the development of
691 novel molecular applications (Chemical Enhanced Saturation Transfer (CEST,
692 PARACEST (De Leon-Rodriguez et al., 2009; Soesbe et al., 2013), Hyperpolarisation
693 techniques...). Despite all these assets, MR techniques lack sensitivity. Thus,
694 molecular imaging possibilities are limited with extremely low compound
695 concentrations (below millimolar). This poor sensitivity may explain the lack of interest
696 for MR investigations on potential EDCs, which can be present in brain structures as
697 traces only and which presence can rarely be measured and quantified with MRI or
698 MR Spectroscopy (MRS) techniques. Interestingly, the MR literature represents an
699 abundant source of knowledge on the potential effects of EDCs and their mechanisms
700 since many studies investigated the dose-effect of various pharmaceuticals albeit not
701 at the very low concentrations encountered in the environment.

702

703 MR biomarkers could benefit knowledge on the endocrine effects of compounds.

704 MRI facilitates the *in-vivo* diagnosis, prognosis and therapeutic monitoring of various
705 brain diseases such as cancer, neurodegenerative diseases and neuropsychiatric
706 diseases (Alzheimer, Parkinson, dementia, epilepsy, multiple sclerosis...). Studies can
707 be performed relatively fast, and longitudinally with little discomfort for patients.
708 Therefore, assessment of repeatability and reproducibility of the outcome can be
709 performed with increased accuracy. MR can also detect various conditions such as
710 stroke and traumatic brain injury, hemorrhage, inflammation and edema.

711 Endocrine disruption also involves metabolic alterations resulting in obesity, diabetes
712 and liver diseases that remain to be understood... Multinuclear applications of MRS

713 and chemical shift imaging (CSI) can be useful for investigating neurometabolic
714 disorders. Moreover, metabolic changes can reveal the very early stages of disease
715 prior to lesion detection (Lei et al., 2009). This is important since EDCs' effects may
716 develop over years and even decades or have consequences in adulthood only.

717 Also, MR investigations demonstrated their usefulness upon assessment of the effects
718 of various compounds (Cherix et al., 2020; Kluza et al., 2011; Padhani and Leach,
719 2005; Wassmuth et al., 2001) both in humans and in animal models. The dose-
720 responses of a variety of MR contrast agents such as gadolinium (Gd)-based contrast
721 agents (Prybylski et al., 2019; Robert et al., 2020; Woodard et al., 2012) or iron oxide
722 nanoparticles, were largely assessed (Diana et al., 2013; Kim et al., 2013). Many other
723 MR studies also investigated the effects of antidepressants (Cherix et al., 2020),
724 antibiotics or analgesics (Bar-Or et al., 2018; Jantzie et al., 2020). MR techniques
725 (Diffusion, Perfusion, blood oxygen level-dependent (BOLD) functional MRI...) can be
726 used to assess the dose-impact of these compounds using surrogate markers of
727 various parameters (permeability, vessel radius, water diffusion, blood volume, blood
728 flow...) that can be mapped on a voxel-by-voxel basis thereby also displaying the
729 heterogeneity and extent of the effects. Moreover, the impact of a defined compound
730 on the behavior or alterations of this behavior can also be investigated with functional
731 MR techniques.

732

733 *Investigating the effects of antidepressants and NSAIDs with MR techniques.*

734 With advanced technological developments in MRI across the past 20 years, BOLD-
735 fMRI and resting-state-(RS)-fMRI became the methodologies of choice for
736 investigating neuropsychiatric disorders. Task-based fMRI has identified altered
737 functional activity in a wide spectrum of psychiatric disorders while RS-fMRI is
738 recognized as a predictor of treatment response in major depressive disorder (MDD),
739 schizophrenia, anxiety disorders and autism where brain connectivity is often altered.
740 fMRI was also extensively used for a better understanding of pain and analgesia-
741 related phenomena (Borsook and Becerra, 2006). There has recently been increased
742 use of RS- fMRI in the context of studies addressing brain network dynamics involved
743 in response to antidepressant and analgesics treatments, both in terms of predicting
744 response to treatment as well as understanding changes in functional brain
745 connectivity after effective treatments. Dichter et al. (2014) reviewed the linkages
746 between RS-fMRI and treatment response in MDD thereby identifying specific

747 biomarkers and specific patterns of brain network dynamics affected by
748 antidepressants. A variety of antidepressant substances that have been increasingly
749 examined with these MR techniques demonstrated to have toxic effects on the
750 reproductive system and hormones (Dichter et al., 2015). This is the case of ketamine,
751 which recently attracted a large interest for its impact on metabolism (Bednarik et al.,
752 2021; Qi et al., 2017). Fluoxetine and norfluoxetine were also abundantly studied with
753 MRI and MRS and are well-known EDCs present in aquatic systems (Mennigen et al.,
754 2011). Moreover, several agents used to correct the endocrine imbalance were also
755 employed as antidepressants such as melatonin and glucocorticoids (Antonioli et al.,
756 2012). Numerous effects of these agents was examined and identified (Kalafatakis et
757 al., 2018). In particular, glucocorticoid receptors are recognized as important targets
758 for EDCs. Of note, important knowledge on the underlying effects of these agents and
759 their potential markers examined with MR techniques was accumulated. An important
760 database exists therefore allowing the identification of risk factors linked to EDCs. In
761 addition, important cohorts of responder and non-responder patients followed over
762 years could serve to examine the long-term effects of a variety of compounds and their
763 mixture. Their physiological and endocrine status is already often followed across
764 years.

765 Neuroimaging techniques have also a considerable role to play in the more appropriate
766 development of analgesics. Most of them only have a significant effect on a minority of
767 patients. Despite the promise of interesting signs of progress, the use of mild
768 analgesics such as paracetamol, ibuprofen and aspirin in the general public and
769 pregnant women increases and is generally perceived to be safe (Thiele et al., 2013).
770 Unfortunately, they also have potent disrupting effects on hormonal homeostasis,
771 leading to congenital malformation in both animals and humans through anti-
772 androgenic mechanisms (Kristensen et al., 2018, 2011). Neuroimaging techniques are
773 usually effective at discriminating responsive and non-responsive patients and reveal
774 novel targets, which could be of value for a better understanding of the endocrine mode
775 of action of these compounds.

776

777 Metabolism and EDCs.

778 EDCs interfere with the endocrine system by altering mechanisms linked to hormone
779 secretion or elimination. EDCs can also mimic hormone action. All these modes of
780 action can disrupt the regulation of general homeostasis of the body and contribute to

781 adverse metabolic phenotypes. EDCs can also predispose patients to several
782 metabolic syndromes and alter nutrient ingestion and metabolism. Moreover, specific
783 individuals may be more affected than others such as the developing fetus, which is
784 more sensitive to endocrine perturbations. Fetus exposure to EDCs may cause
785 irreversible effects that may become detectable later in life. In this context, MRS can
786 be useful. An example was given by Kunz et al. (2011) who used proton MRS at 9.4T
787 to assess the effect of perinatal exposure to bisphenol A (BPA) on cerebral structural
788 development and metabolism after birth in rat pups. On postnatal day 20, *in vivo*
789 metabolite concentrations in the rat pup hippocampus were measured. Exposure to
790 low dose BPA during gestation and lactation resulted in subtle and regional neuronal
791 and glial alterations in brain development in offspring. Furthermore, BPA exposure led
792 to significant changes in the Glutamate to Aspartate ratio in the hippocampus, which
793 is postulated to reflect impaired mitochondrial function and probably implicates a
794 reduced ability of the brain to oxidize glucose especially in conditions of elevated
795 energetic demand (Kunz et al., 2011). The changes observed after prenatal BPA
796 exposure will likely imply long-lasting effects on cognitive development and function.
797 While such studies are needed and somehow not difficult to realize, investigations of
798 EDCs effects in huge cohorts of humans may benefit the assessment of the levels of
799 exposure to EDCs. Such screening studies can be performed with NMR metabolomics
800 and were proposed by the EDCMET project (Küblbeck et al., 2020). Using serum NMR
801 platforms, NMR spectroscopy can simultaneously quantify 230 metabolic features
802 such as serum proteins, lipids, fatty acids, glycolysis substrates, amino acids, ketone
803 bodies and many other molecules to obtain signature metabolic profiles affected by
804 EDCs.

805 Although few MR studies have been conducted yet in the context of pharmaceutical
806 EDCs, the specific case of MR contrast agents can illustrate the potential of MRI and
807 MRS for the detection and evaluation of endocrine disruption.

808 Gd is a heavy metal of the lanthanide group. Chelated forms of Gd are used in MRI
809 and MR angiography to avoid the toxicity of Gd³⁺. Recently, tissue deposition of Gd
810 was demonstrated in various rodent and human tissues of the body (Sato et al., 2013;
811 Wáng et al., 2015) and of the brain (Gulani et al., 2017). Free Gd³⁺ ions induced cell
812 death, oxidative stress and accumulation of reactive oxygen species (ROS) in rat
813 cortical neurons (Feng et al., 2011). Briner et al. (2000) reported important behavioral
814 responses of mice exposed to lanthanides with consequences on their development

815 further confirmed by Feng et al. (2006) who also showed altered DNA and protein/DNA
816 concentrations in the brain. Interestingly, the current literature does not report
817 longitudinal BOLD-fMRI or perfusion studies in animal models or humans combined
818 with behavioral assessments following Gd injections although 30 million doses are
819 consumed each year (Guo et al., 2018). Non-invasive functional evaluations could be
820 insightful as predictive factors of parkinsonism since Gd deposition in the dentate
821 nucleus and the globus pallidus induced symptoms (Welk et al., 2016) but require long-
822 term follow up. In the context of EDCs, cell cultures demonstrated that toxic effects on
823 thyroid hormones depended on the chemical structure and dose of Gd- based contrast
824 agents (Ariyani et al., 2016) but no *in-vivo* study has been conducted to date. Again,
825 as described earlier for other pharmaceuticals, Gd-based contrast agents are difficult
826 to remove with the usual sewage treatment technology. Amounts of Gd-based contrast
827 agents in wastewater significantly increased with the increasing use of MRI technology
828 (Brünjes and Hofmann, 2020; Inoue et al., 2020) emphasizing the need to change
829 medical practices.

830 More recently, manganese ions (Mn^{2+}) attracted overwhelming interest owing to their
831 paramagnetic properties enabling them to be used as contrast agents and to depict
832 the rodent brain cytoarchitecture with unprecedented dose-dependent MR contrast. A
833 better understanding of their toxicity was also obtained using MRS (Just et al., 2011;
834 Just and Gruetter, 2011). Mn-induced neurotoxicity is well known with reference to
835 occupational Mn exposure. Due to the risk exposure of smelters and welders, it was
836 shown that Mn-exposure disrupted the endocrine systems of Mn-exposed workers
837 (Long et al., 2014). Mn uptake was reported in various human brain structures (caudate
838 nucleus, substantia nigra, pituitary gland, ventromedial hypothalamus...). A wealth of
839 human studies demonstrated that significant hyperintensities in T1-weighted MR
840 images of Mn-exposed workers occur (Criswell et al., 2019). Various MR
841 methodologies can be used to identify Mn toxicity: the pallidal index (PI) can be used
842 to quantify hyperintensities due to increased Mn^{2+} concentrations but relaxometry may
843 also quantify Mn content while proton MRS can be useful in detecting the impact of Mn
844 on metabolites (Just et al., 2011). Notably, metabolites can be markers of Mn-induced
845 Parkinson or encephalopathic symptoms (Peres et al., 2016).

846 Many other metal compounds play a role as EDCs (reviewed in Iavicoli et al. (2009)).
847 MRI/MRS can identify the influence of these metals on the endocrine system by
848 exploring their mechanisms of action, their content or their effects on behavior. Iavicoli

849 et al (2009) also pointed at the lack of studies on the effects of mixtures of these metals.
850 Some of them such as Zinc (Zn) or Europium (Eu) or copper (Cu), iron (Fe³⁺) can also
851 be used in the chemical structure of contrast agents .In an identical manner to Gd-
852 based compounds, metal compounds used in the medical practice find their way to
853 rivers, where they may have deleterious effects on invertebrates and vertebrates
854 (Iavicoli et al., 2009).

855 In conclusion, the *in-vivo* detection of EDCs' amounts and an improved understanding
856 of their mechanisms and modes of action are much needed to validate the associated
857 risks factors and determine appropriate predictive markers. But this is challenging.
858 Magnetic Resonance techniques can represent a major tool in this context with long-
859 term accumulated data and already developed methodologies that just need to be
860 used.

861

862 **7. Discussion**

863

864 *Are pharmaceutical drugs endocrine disruptor compounds?*

865 The pharmaceutical drugs considered in this article (antibiotics, antidepressants, anti-
866 inflammatories) induce neural effects. Whether all these neural effects occur through
867 an endocrine disrupting mode of action still needs to be thoroughly documented, in
868 particular at doses close to the environmental exposure. There are, however, several
869 evidences highlighted in this article that suggest that these substances may act as
870 endocrine disruptors.

871

872 For antibiotics, the evidences in favor of an endocrine disrupting mode of action are
873 provided by the studies performed in aquatic models and using low environmentally
874 relevant doses of these substances. In fish, exposure to these molecules impaired
875 reproduction probably through modifications of the gonadotropic axis and
876 steroidogenesis (Kim et al., 2017, 2012). The thyroid axis was also targeted leading to
877 affected growth and development (Yu et al., 2020). In mammals, such studies are still
878 lacking. In particular, whether the effects induced by exposure to antibiotics on social
879 and mood behaviors in children (Slykerman et al., 2017) and animal models (Degroote
880 et al., 2016; Leclercq et al., 2017; Tochitani et al., 2016) involve a disruption of
881 neuroendocrine systems needs further investigation. It is, however, important to keep

882 in mind that these behaviors are known to be regulated by sexual and thyroid
883 hormones.

884

885 The SSRIs antidepressants such as fluoxetine or sertraline, the most commonly
886 prescribed ones, showed to affect social, anxiety-related and reproductive behaviors
887 in aquatic species after developmental exposure to doses compatible with
888 environmental contamination (Sehonova et al., 2018). Such alterations suggest
889 endocrine disruption effects triggering the hypothalamic-pituitary-adrenal and
890 gonadotropic axis (Mennigen et al., 2011). For human assessment of the risk
891 associated with developmental antidepressant exposure, the literature deals with
892 developmental exposure to SSRIs at pharmacological doses, in the context of maternal
893 treatment for major depressive disorder during pregnancy and/or postpartum
894 depression. Studies in rodents report long-lasting endocrine and behavioral alterations
895 on the developmentally exposed offspring, and neural alterations are described,
896 susceptible to be responsible for these long-term effects. In the study of Soiza-Reilly
897 et al. (2019), it was shown that all the inhibitors tested exerted endocrine disrupting
898 effects, with different mechanisms from one molecule to another. Therefore, potential
899 effects of SSRIs as endocrine disruptors at environmental doses have to be
900 investigated on mammal models.

901

902 The NSAIDs interfere with the E2 dependant mechanisms during brain development.
903 One of the numerous actions of E2 signal is to activate COX-1 and COX-2 enzymes
904 for the conversion of Arachidonic Acid to PGE2 (Hermenegildo et al., 2006). PGE2
905 have a key role in the brain sexualization by regulating the male differentiation of the
906 preoptic area and cerebellum (Amateau and McCarthy, 2004, 2002). So, the inhibition
907 by NSAIDs of COX enzymes and consequently of PGE2 production during CNS
908 development results in a reduction of sexual behaviour, play behavior, and of the
909 sensory threshold as well as an increase of object exploration time in adult male
910 (Amateau and McCarthy, 2004; Dean et al., 2012). At the cellular level, NSAIDs impact
911 the morphology of neuronal and microglial cells by inhibiting spinophilin production, a
912 protein specific to dendritic spines (Amateau and McCarthy, 2004, 2002; Lenz et al.,
913 2013). Since microglia produce prostaglandins, express prostaglandin receptors, and
914 are activated during the critical period for sexual differentiation, some authors have
915 hypothesized a role of microglia in E2-induced PGE2 production in the POA (Welberg,

916 2013). Microglial PGE2 has been shown to play an important role in the proliferation of
917 astrocytes, identifying PGE2 as a key neuro-inflammatory molecule that triggers the
918 pathological response related to the uncontrollable proliferation of astrocytes (Zhang
919 et al., 2009). These results are important to elucidate the role of activated microglia
920 and PGE2 in astrocyte proliferation and to suggest a potential disturbance in chronic
921 exposure to anti-inflammatory agent molecules.

922

923 Even if reported studies in this review have used pharmacological doses, whether
924 antibiotics, antidepressants and anti-inflammatories induce adverse effects on the
925 central nervous system development at environmental exposure remains to be
926 answered.

927

928 Pharmaceutical drug exposure and susceptibility to neurodegenerative disease, what
929 about epigenetic?

930 The epigenome is responsible for the functional use and stability of information within
931 the genome, but in contrast to the stable genetic material, the epigenome fluctuates in
932 response to environmental exposures. Pharmaco-epigenetics is an emerging aspect
933 of the usual pharmaco-vigilance. It concerns alterations in gene expression of drug-
934 metabolizing enzymes and transporters that result in interindividual variations in drug
935 responses. During the developmental period from newborn to childhood, inter-
936 individual variations are combined with changes related to the differentiation and
937 growth of tissues and organs. All are under epigenetic control, and therefore sensitive
938 to epigenetic deregulations. As previously mentioned, about nothing is known about
939 relationships between epigenetic and pharmaceutical pollutants (i.e. low-doses and
940 long exposures). However, there is growing evidence suggesting such relationships.
941 (1) Brain development and neuro-degenerative diseases are under epigenetic control.
942 Indeed, individuals with neuropsychiatric and neuro-degenerative diseases display
943 epigenetic brain programming disturbances (Abdolmaleky et al., 2008). Studies of
944 monozygotic twins discordant for schizophrenia and bipolar disorders reveal a
945 significant difference in DNA hypomethylation of gene networks and pathways directly
946 relevant to psychiatric disorders and neurodevelopment. Analyses of *post-mortem*
947 brain tissues reveal DNA hypomethylation in psychosis patients (when compared to
948 controls), for the same DNA regions than those identified in twins (Dempster et al.,
949 2011). Brain masculinization is a consequence of testosterone production which

950 epigenetically regulates sex differences in the neuronal structure of some
951 hypothalamus nuclei (McCarthy et al., 2009). (2) Pharmaceutical drug exposure alters
952 epigenetic pathways of brain development. Indeed, *in utero* exposure to many
953 substances results in neuronal injury related to epigenetic changes and results in long-
954 term neuro-developmental impairment in the offspring. More, transgenerational
955 epigenetics may also explain the fact that developmental abnormalities, impairment in
956 learning and memory, and attention deficit can occur even in the absence of direct fetal
957 exposure, when drugs are used prior to conception (Neri et al., 2015). (3) The
958 consequences of intrauterine exposure to drugs can appear very late, at adolescence
959 or adulthood. As an example, prenatal exposure to xenobiotics probably leads to
960 alteration of the hypothalamic-pituitary-adrenal (HPA) axis. These alterations are
961 believed to increase the susceptibility to adult neuropsychiatric disorders (such as
962 depression and schizophrenia). Among the possible mechanisms of action,
963 xenobiotics can directly induce epigenetic alterations, modifying the expression of main
964 fetal genes (such as hippocampal glucocorticoid receptor, adrenal steroidogenic acute
965 regulatory protein...) (Zhang et al., 2014).

966

967 To conclude, it appears essential to keep in mind that epigenetic deregulations are a
968 powerful way to account for time-lagged and even transgenerational effects, often
969 observed in neurodegenerative pathologies and could be crucial to validate the
970 involvement of environmental pollutants at their onset (during childhood or later in life).

971

972 Alternative methods for the assessment of the impact of endocrine disruptor
973 compounds on the central nervous system:

974 A large set of MR-based data and know-how has been accumulated across years to
975 evaluate brain dose-responses to various pharmaceuticals. This knowledge could be
976 advantageous to evaluate *in-vivo* the impact of various molecules acting as EDCs.
977 Long-term follow-up of changes in behaviour, neuroanatomy, function and metabolism
978 of EDC-exposed populations could be envisaged and associated with various
979 measurements in drinking water or sewage. Moreover, important databases of the
980 effects of antidepressants, antibiotics and NSAIDS on brain function and metabolism
981 exist and could be helpful for modelling purposes. Although novel methods exist, one
982 important disadvantage of MR techniques is their low sensitivity, which does not permit
983 the detection of traces or very low doses of pharmaceuticals, impeding reliable and

984 direct attribution of longitudinal changes to specific molecules considered as EDCs.
985 Nevertheless, MR can be efficiently coupled to other imaging modalities such as
986 ultrasound, CT or PET, which have molecular imaging possibilities. Nowadays, PET-
987 MRI is a well-accepted technique both in rodents and humans allowing the coupling of
988 the molecular potential of PET to the high spatial resolution of MRI (Musafargani et al.,
989 2018) with little-invasiveness and could be effective at EDC detection at very low
990 doses. While *in vivo* analysis is of paramount importance, the use of MR microscopy
991 and MR spectroscopy to evaluate *ex-vivo* and *in-vitro* specimens is not to be neglected.
992 In this regard, one can think of the systematic and longitudinal analysis of water
993 samples with high-resolution MR techniques (HR MAS) (Lucas-Torres and Wong,
994 2019), which could reveal the presence of various substances and can be coupled to
995 mass-spectroscopy techniques (Emwas, 2015).

996

997 **8. Conclusion**

998

999 Scientific literature reported in this review shows real adverse effects of pharmaceutical
1000 products present in the environment on the development of the central nervous system.
1001 The risk for future generations could be a concern and has to be evaluated. Indeed,
1002 food and water for human consumption are contaminated and the exposure to these
1003 pharmaceutical substances occurs during the adult life but also at earlier stages
1004 including foetal development. The chronic exposure to these drugs even at
1005 environmental doses for human but also farm animals and wild life is, at this time,
1006 largely underestimated. Metrology studies have to be multiplied to measure these
1007 pharmaceuticals in the whole environment (macro and microenvironment) to define our
1008 exposome and evaluate the risk of this environmental exposure. The question of the
1009 implication of the microbiota is emerging, futures studies have to precise if these drugs
1010 exert their adverse effects on the CNS development by disrupting the gut-brain axis.

1011

1012 **9. Bibliography**

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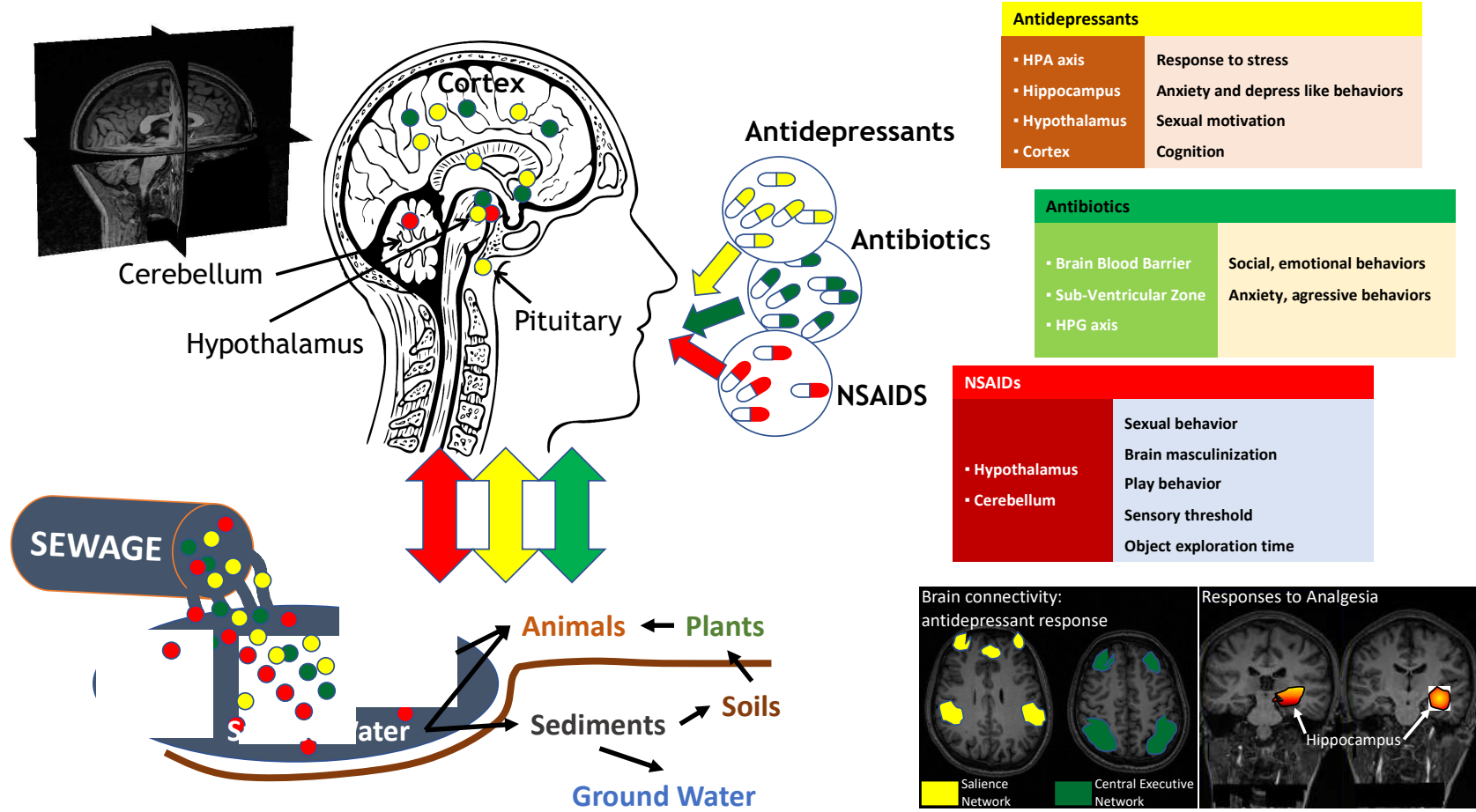
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1786 **Graphical Abstract Caption**

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1788 Ingested pharmaceutical drugs have therapeutic effects on the brain that have been
1789 widely characterized with invasive and non-invasive techniques. A number of these
1790 molecules have known endocrine effects. Among the most used therapeutic
1791 compounds, antidepressants, antibiotics and NSAIDs account for a large percentage.
1792 They are excreted via urine and feces and can be found at environmental doses in the
1793 sewage and the wastewater, where they affect aquatic milieux and can be re-
1794 absorbed by humans. They become potential endocrine disruptor compounds. What
1795 are their neural effects and mechanisms? How can they be measured? Can
1796 neuroimaging techniques contribute to the efforts for a better assessment of endocrine
1797 risk factors with their accumulated knowledge and non-invasive markers (Connectivity
1798 studies, fMRI, MR Spectroscopy...)? The present review addresses the current status
1799 and needs of research on pharmaceutical pollutants with endocrine-disrupting modes
1800 of action.