1   **The aversive brain system of teleosts: Implications for neuroscience and biological psychiatry**

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11   **Abstract**

12   Defensive behavior is a function of specific survival circuits, the "aversive brain system", that are

13   thought to be conserved across vertebrates, and involve threat detection and the organization of de-

14   fensive responses to reduce or eliminate threat. In mammals, these circuits involve amygdalar and

15   hypothalamic subnuclei and midbrain circuits. The increased interest in teleost fishes as model or-

16   ganisms in neuroscience created a demand to understand which brain circuits are involved in defen-

17   sive behavior. Telencephalic and habenular circuits represent a "forebrain circuit" for threat pro-

18   cessing and organization of responses, being important to mounting appropriate coping responses.

19   Specific hypothalamic circuits organize neuroendocrine and neurovegetative outputs, but are the

20   less well-studied in fish. A "midbrain circuit" is represented by projections to interneurons in the

21   optic tectum which mediate fast escape responses via projections to the central gray and/or the

22   brainstem escape network. Threatening stimuli (especially visual stimuli) can bypass the "high

23   road" and directly activate this system, initiating escape responses. Increased attention to these cir-

24   cuits in an evolutionary framework is still needed.

25   *Keywords:* Fear; Anxiety; Aversive brain system; Comparative neuroanatomy; Teleost fish

1. Introduction

Defensive behavior is a function of specific survival circuits that are highly conserved across vertebrates (LeDoux, 2012), and involve threat detection, as well as the organization of species-specific defensive responses to reduce or eliminate threat (LeDoux, 2012). In mammals, these circuits involve sensory systems that detect conditioned and unconditioned threatening stimuli, amygdalar circuits that select appropriate behavioral and neuroendocrine responses and promote aversive learning, hypothalamic circuits for both defensive behavior and neuroendocrine responses, and midbrain circuits that control the output (LeDoux, 2012). This survival circuit for defensive behavior links this appraisal phase, in which the global organismic state is determined based on threat detection, to a response phase, in which "the instrumental physiological and behavioural responses are determined and executed" (Andersen et al., 2016, p. 5). Different threat levels restrict attention "in the current global organismic state [to make] the organism focus on a short-term motive to […] survive a threat" (Andersen et al., 2016, p. 6).

In fish, defensive circuits have not been thoroughly described, but there is an increasing awareness that defensive behavior is a fundamental function in these animals (Andersen et al., 2016; Kalueff et al., 2012; Kittilsen, 2013). As a result, fish are increasingly being used in neurobehavioral research (Gerlai, 2014; Hall et al., 2014; Kalueff et al., 2014b; Stewart et al., 2015). A framework for establishing homologies for defensive circuits in fish, therefore, is useful for this enterprise. Classical neuroscientific approaches to describing behavioral circuits involve the demonstration that a given structure is activated (or inhibited) by specific stimuli or behavioral paradigms, as well as the effects of lesioning (or silencing) and stimulating the structure. Even though there are many technical difficulties in performing functional neuroanatomy in the diminutive zebrafish, novel genetic techniques (Friedrich et al., 2010) have allowed important discoveries regarding the limbic system.

51   The increase in the use of zebrafish (Kalueff et al., 2014a) and other species (Hall et al.,

52   2014) as organisms in behavioral models for anxiety- and fear-like behavior also prompted the need

53   to describe the neural structures that are involved in these behaviors (Guo et al., 2012). While the

54   unspoken assumption in the field appears to be one of "multiple realizability" (Bickle, 2010) – in-

55   cluding the idea that it is the behavioral function that needs to be similar, and not the brain circuits

56   underlying it, in order to use these assays as models in psychopathology (Wright, 2002) –, at least

57   from an evolutionary point of view it is interesting to assess whether the putative conservation of

58   behavioral responses to aversive stimuli is accompanied by conservation of the neural substratum

59   (Striedter et al., 2014). The present article reviews the circuitry that is involved in detecting, identi-

60   fying, processing, and responding to threat in fish, with a special focus on zebrafish models.

61

2. Discovering neural circuits for aversive behavior in fish

63   An important starting point in determining the aversive behavior network in zebrafish is ac-

64   tivation studies. Typically, this is done by examining immediate early gene products, such as the

65   *cfos* gene and its protein, c-Fos. A network comprised of the medial nucleus of the dorsal telen-

66   cephalon (Dm), ventral nucleus of the ventral telencephalon (Vv), supracommissural nucleus of the

67   ventral telencephalon (Vs), and preoptic region (POA) shows upregulated *cfos* expression after ex-

68   posure to conspecific alarm substance [CAS] (Faustino et al., 2017). The expression of c-Fos during

69   CAS exposure appears to be specific, as no increases were observed in the lateral nucleus of the

70   dorsal telencephalon (Dl), dorsal nucleus of the ventral telencephalon (Vd), habenula, or thalamus

71   (Ruhl et al., 2017). Dm is also activated after exposure to the light/dark test (Lau et al., 2011; von

72   Trotha et al., 2014), an anxiogenic stimulus for zebrafish (Maximino et al., 2010a). Thus, it appears

73   that a network involving Dm, Vv, Vs, and POA is involved in detecting and/or processing aversive

74   stimuli and/or selecting behavioral strategies in zebrafish. A network for the retrieval of fear memo-

75   ries include Dm, Dl, and thalamus, as these structures showed c-Fos expression during presentation

76   of a red light that has been previously associated with CAS (Ruhl et al., 2017).

77   Other aversive stimuli have also been used to investigate threat detection and processing in

78   zebrafish larvae. A looming stimulus, which simulates predatory attack, activates neurons in the op-

79   tic tectum (Dunn et al., 2016; Temizer et al., 2015). Tyrosine hydroxylase-positive neurons in the

80   caudal hypothalamus (Hc) respond to aversive stimuli, including pH change, high ammonia, and

81   handling stress (Semenova et al., 2014). Using immunohistochemical detection of phosphorylated

82   extracellular signal-regulated kinase (pERK), Randlett et al. (2015) mapped the activity of nuclei in

83   the larval brain in response to different aversive stimuli (exposure to mustard oil, dish taps, heated

84   water, electric shocks). The authors found that while each stimulus promoted pERK activity in spe-

85   cific regions (due to the diversity of sensory channels tapped by each stimulus), all four activated

86   the locus coeruleus, caudal hindbrain, Hc, POA, and subpallium. It is not clear whether the subpal-

87   lial regions observed in this experiment overlap with those found in CAS-exposed adults (i.e., Vv

88   and Vs); nonetheless, these results suggest a wider network that is specialized in the detection of

89   aversive stimuli which includes pallial and subpallial components of the amygdala homologues, the

90   neuroendocrine hypothalamus, optic tectum, locus coeruleus, and the brainstem escape network.

91   The focus of this review will now turn to each of these foci. We will quickly review some of

92   the evidence for proposing these areas as full or partial homologues of specific mammalian nuclei

93   which have been implicated in defensive behavior. Importantly, we will review evidence for the

94   participation of these regions in aversive behavior in fish, and delineate, when possible, the circuitry

95   that is involved in these roles.

96

97   **3. Pallial and subpallial components of the teleostean amygdala**

98   The fact that the teleostean telencephalon is everted precluded, for a long time, the easy es-

99   tablishment of homologies for telencephalic structures (Nieuwenhuys, 2011). Different eversion

100   models lead to different proposed final topologies of pallial structures in adult fish (Braford, 2009;

101   Butler, 2000; Mueller et al., 2011; Nieuwenhuys, 2011; Northcutt, 2008; Wullimann and Mueller,

102   2004; Yamamoto et al., 2007); as a result, different propositions have been made regarding amyg-

103   dala homologues in zebrafish. Based on topology and topography, cytoarchitectonics, neurochem-

104   istry, expression of developmental regulatory genes, and behavioral data, we will follow our previ-

105   ous proposal that the medial nucleus of the dorsal telencephalon (Dm) is homologous to the "limbic

106   associative" amygdaloid system (lateral and basolateral amygdala of mammals), while the subcom-

107   missural and postcommissural nuclei of the ventral telencephalon (Vs and Vp, respectively) are ho-

108   mologous to the "autonomic" amygdaloid system (central extended amygdala [CEXA]) (Maximino

109   et al., 2013a)(Figure 1A).
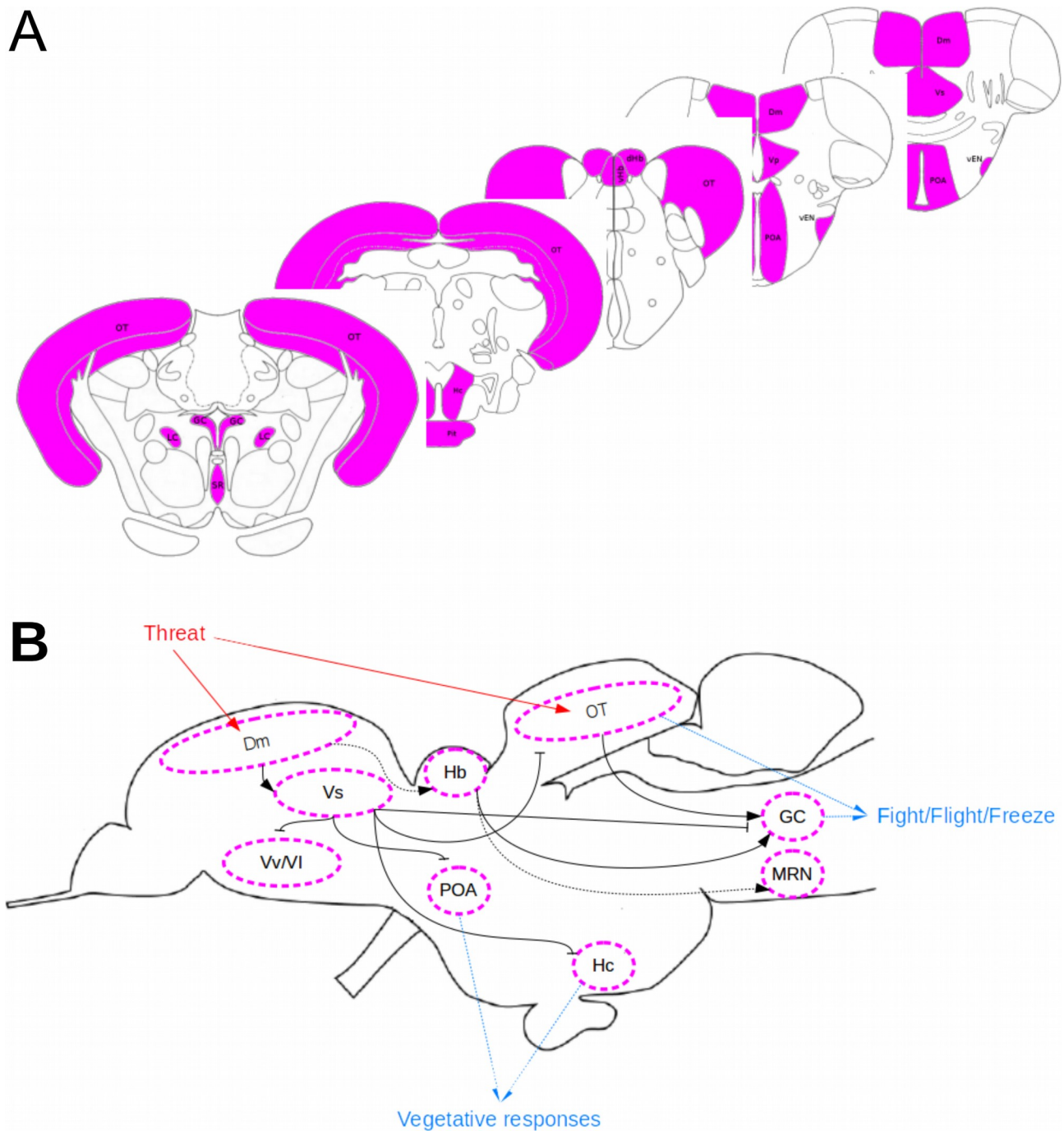
Figure 1: (A) Frontal view of the zebrafish brain circuits for threat detection, identification, and processing, and response selection (in purple), described in Fig. 1B. The right-to-left plans represent the rostrocaudal axis. Schemes adapted from Wulliman et al., 1996. (B) Circuits for threat detection, identification, and processing and response selection in the teleost brain. The dorsomedial telencephalon (Dm) is homologous to the frontotemporal amygdala system, and is the entry for the "forebrain circuit" that terminates in the mesencephalic central gray (GC) and in the hypothalamic circuits for neurovegetative responses (POA, Hc). An indirect projection is also depicted for the ventral habenula (Hb); this projection involves a feedforward glutamatergic projection from the Dm to the entopeduncular nucleus, and from there to the ventral habenula. This can represent part of a habenular circuit in the forebrain circuit which projects indirectly to the raphe (MRN) serotonergic neurons via glutamatergic interneurons in the interpeduncular nucleus and raphe (not shown). The "midbrain circuit" is represented by projections to interneurons in the optic tectum (OT) which mediate fast escape responses via projections to the GC and/or the brainstem escape network (not shown). Threatening stimuli (especially visual stimuli) can bypass the forebrain circuit and directly activate this system, initiating "quick-and-dirty" escape responses.

Abbreviations: Dm: medial nucleus of the dorsal telencephalon; Vs: supracommissural nucleus of the ventral telencephalon; Vv: ventral nucleus of the ventral telencephalon; Vl: lateral nucleus of the ventral telencephalon; Hb: habenula; POA: preoptic area; Hc: caudal hypothalamus; OT: optic tectum; GC: central gray; MRN: median raphe nucleus.

Full black arrows: direct projections; dashed black arrows: indirect projections. Arrows terminating in dimension lines (⊣) represent inhibitory projections. Blue arrows represent outputs, while red arrows represent inputs.

111   Lesion studies implicated the Dm in associative learning of aversive memories in goldfish.

112   Ablation of the Dm, but not of the Dl, impair the acquisition and maintenance of two-way (active)

113   avoidance acquisition in this species (Portavella et al., 2004b, 2004a, 2002; Portavella and Vargas,

114   2005). c-Fos studies with zebrafish have also suggested a role for the Dm in aversive conditioning:

115   the association between a red light and CAS produces conditioned responses to the light that are

116   very similar to the innate repertoire of zebrafish (Hall and Suboski, 1995a, 1995b; Ruhl et al.,

117   2017). Interestingly, during the acquisition phase (when the red light and the CAS are presented to-

118   gether), the number of c-Fos-positive cells is higher in the Dm, but not in the lateral nucleus of the

119   dorsal telencephalon (Dl, the hippocampal homologue; Goodson & Kingsbury, 2013) or in the dor-

120   sal nucleus of the ventral telencephalon (Vd, the striatum homologue; Ganz et al., 2011). 24 h later,

121   during the retrieval phase (when only the red light is presented), c-Fos-positive cells are increased

122   in the Dm, Dl, and thalamus (Ruhl et al., 2017). In any case, it appears that the Dm is involved in

123   both the acquisition and the maintenance of aversive memories in cyprinids.

124   The majority of neurons in pallial regions are glutamatergic (von Trotha et al., 2014), with

125   some GABAergic interneurons. Lal et al. (2018) produced *Gal4FF* zebrafish lineages driving the

126   expression of the botulinum toxin B light chain (BoTxBLC) gene that showed deficits in active

127   avoidance conditioning. Among these lineages, two showed expression limited to the Dm, and in

128   both the trapped gene was *emx3*. In addition to showing deficits in conditioned aversive behavior,

129   these animals also showed changes in their response to CAS, with decreased freezing but increased

130   erratic swimming. Only 16% of the cells in the Dm express the Gal4FF construct, and the majority

131   are neurons; 94% of these neurons are glutamatergic. These neurons project heavily to the hypothal-

132   amus, including anterior tuberal nucleus (ATN), lateral hypothalamic nucleus (LH), and dorsal zone

133   of the periventricular hypothalamus, as well as to telencephalic regions (entopeduncular nucleus,

134   preoptic area, Vd, and Vs)(Figure 1B), suggesting neural networks involved in both conditioned and

135   unconditioned aversive behavior (Lal et al., 2018).

136   The role of the Dm in unconditioned behavior has also been assessed. In zebrafish, exposure

137   to the light/dark test increases c-Fos expression in the Dm (Lau et al., 2011; von Trotha et al.,

138   2014). Moreover, CAS exposure also increases *cfos* in the Dm of zebrafish (Faustino et al., 2017),

139   suggesting that ethologically-relevant aversive stimuli recruit these cells even when conditioning is

140   not involved. As already discussed, expression of BoTxBLC in a subset of Dm neurons in zebrafish

141   decreases freezing responses and increases erratic swimming after CAS exposure (Lal et al., 2018).

142   A participation in restraint stress-induced behavioral responses has also been suggested. In Nile

143   tilapia (*Oreochromis niloticus*), restraint stress increases 5-HT metabolism in the Dm (Silva et al.,

144   2014). Likewise, acute stress (lowering water levels) increases *htr1aa* and *htr1ab* expression in the

145   Dm of rainbow trout (Vindas et al., 2017); interestingly, 5-HIAA levels were increased in the Dm

146   only in those animals which were classified as "proactive" in relation to a behavioral response to

147   hypoxia (Vindas et al., 2017), suggesting that 5-HT acts in this nucleus to mount active responses to

148   remove stressors and restore homeostasis. Moreover, destroying 5-HT fibers in the telencephalon

149   with the serotonergic toxin 5-7-DHT decreases the ratio of correct avoidance responses in an active

150   avoidance paradigm in zebrafish (Amo et al., 2014). Thus, feedback mechanisms from neuromodu-

151   lators appear to also be important in these responses (Table 1). Consistent with the hypothesis of a

152   role of the Dm in active responses to aversive stimuli, inhibition of the Dm in *Leporinus macro-*

153   *cephalus* by injecting midazolam, an anxiolytic and sedative benzodiazepine (Dundee et al. 1985),

154   abolished stress-induced analgesia (Wolkers et al., 2015).

155

Table 1 – Neuromodulatory (monoaminergic) innervation of nuclei in the aversive brain system of teleosts. Given that monoaminergic regions such as the raphe are important targets of forebrain and midbrain circuits, it is likely that modulating the activity of these neuromodulators represent ways to "fine-tune" defensive responses, including by feedback. The number of '+' symbols represent the relative amount of innervation in these regions.

Abbreviations: 5-HT: serotonin; DA: Dopamine; NE: noradrenaline; Dm: medial nucleus of the dorsal telencephalon; Vs: supracommissural nucleus of the ventral telencephalon; Vv: ventral nucleus of the ventral telencephalon; Vl: lat-

eral nucleus of the ventral telencephalon; vEN: ventral entopeduncular nucleus; Hb: habenula; POA: preoptic area; Hc: caudal hypothalamus; OT: optic tectum; GC: central gray.

	5-HT innervation	DA innervation	NE innervation
Dm	+	0	
Vs	+	+	++
Vv	+	++	++
Vl	+	+	++
vEN	++	0	?
Hb	++	0	0
POA	+++	++	+
Hc	+++	+++	+
OT	++	++	+
GC	+++	?	?

156

157   In rodents, different components of the limbic associative amygdalar system mediate re-

158   sponses innate stimuli (auditory and visual components of predator cues) vs. conditioned stimuli

159   (i.e., stimuli which were previously paired with noxious stimuli)(Gross and Canteras, 2012). In

160   mammals, olfactory components of predator cues bypass the cortical components of the amygdala,

161   instead projecting directly to subcortical components (posteroventral part of the medial amygdala;

162   Gross and Canteras, 2012). These different components process distinct afferent inputs and channel

163   them to parallel downstream efferent pathways, responsible for output circuits for fear of predators

164   and fear of pain (Gross and Canteras, 2012). In zebrafish, sensory input to the posterior telen-

165   cephalon (including Dm) suggest massive olfactory information (e.g., Miyasaka et al., 2014), while

166   visual and auditory stimuli are processed initially in the optic tectum (Northcutt, 1983; Meek,

167   1990); however, the fact that an olfactory stimulus can be associated with a visual stimulus in the

168   Dm (Ruhl et al., 2017; Lal et al., 2018) suggests the participation of a projection from the optic tec-

169   tum, possibly via the lateral preglomerular nucleus (Carr, 2015). Thus, in zebrafish the Dm also ap-

170   pears to be important for learned fear, but the participation in unconditioned behavior suggests that

171   either subpopulations of the Dm process different stimuli, or that the evolutionary shift towards vis-

172   ual and auditory stimuli in mammals displaced the massive olfactory projections that was found in

173   fish.

174   If there is considerable evidence for the homology between Dm and the limbic associative

175   amygdala of mammals, this is not the case for the homology between Vs/Vp and the autonomic

176   amygdala; in fact, it is more probable that these regions are only *partially* homologous to the CEXA

177   (Goodson and Kingsbury, 2013; Maximino et al., 2013a). In mammals, the CEXA has been pro-

178   posed to mediate the selection of vegetative and behavioral responses to threatening stimuli (Gozzi

179   et al., 2010; LeDoux and Pine, 2016), as well as conditioned fear (Ciocchi et al., 2010; Haubensak

180   et al., 2010; LeDoux, 1998). The circuit acts by tonically inhibiting downstream responses mediated

181   by the periaqueductal gray area (PAG) and hypothalamus (freezing, flight), or by the basal forebrain

182   (risk assessment); inhibition of these circuits (by, e.g., signals from the "limbic associative" amyg-

183   dala) release behavior in one of these two streams, producing appropriate active or passive re-

184   sponses to the threatening stimulus (Maximino, 2012). In zebrafish, these neurons are also

185   GABAergic (Mueller and Guo, 2009), suggesting a similar circuit.

186   Almost no behavioral evidence exists for the role of Vs/Vp in defensive behavior. One of

187   the possible reasons is that the Vs and Vp are continuous with the Vd in a rostrocaudal axis, leading

188   authors to report effects (or lack thereof) of interventions in wrongly identified structures. One im-

189   portant exception is the observation that CAS increases *cfos* expression in the Vs (Faustino et al.,

190   2017). Interestingly, as reported above, this work also found increased *cfos* in the Dm, Vv, and

191   POA. Importantly, control animals showed functional connectivity between these regions, while ex-

192   posure to CAS decreased these correlations; in fact, animals exposed to CAS showed only co-acti-

193   vation of Dm-Vs and Vv-Vs (Faustino et al., 2017). The precise mechanism for this decreased co-

194   herence is yet to be described; however, considering the equivalent mammalian circuit, it is possible

195   that activation of the Dm activates inhibitory neurons from the Vs, which could be responsible for

196   decreased connectivity with Vv and POA, while at the same time disinhibiting downstream (hy-

197   pothalamic and mesencephalic) mechanisms for response emission (Figure 1B).

198   In summary, the Dm appears to be important for both conditioned and unconditioned aver-

199   sive responses, as well as to mounting appropriate (active vs. passive) responses. The Vs also ap-

200   pears to participate in processing unconditioned threat, but its role in response selection and learn-

201   ing is still unknown.

202

203   **3. Does the habenula participate in defense?**

204   The habenulae are paired structures located in the roof of the rostral diencephalon of fishes,

205   divided classically into a dorsal, asymmetric portion (dHb) and a ventral, symmetric portion (vHb).

206   The dHb can be further subvidided into medial and lateral subnuclei (Aizawa et al., 2011; Okamoto

207   et al., 2011, 2008), although eleven subdivisions (Hb01 - Hb10) are suggested by single-cell RNA-

208   Seq registered to anatomy (Pandey et al., 2018). Four clusters were identified in the zebrafish vHb

209   (Hb11, Hb12, Hb13, and Hb15), based on the expression of genetic markers and signaling

210   molecules (Pandey et al., 2018). The vHb receives (putatively glutamatergic) projections from the

211   ventral portion of the entopeduncular nucleus (vEN) (Okamoto et al., 2011; Amo et al., 2014),

212   which by its turn receive excitatory projections from the Dm (Lal et al., 2018); as a result, a

213   excitatory feedforward circuit exists from Dm to vEN to vHb.

214   The difference in size between left and right habenulae is due mainly to the enlargement of

215   the lateral subnucleus (dHbL) in the left habenula in relation to the right, which shows an enlarged

216   medial subnucleus (dHbM) (Amo et al., 2010; Okamoto et al., 2011). This difference correlates with

217   parapineal asymmetry (Gamse et al., 2003) and is concordant with the lateralization of viscera

218   (Barth et al., 2005; Domenichini et al., 2011) and subsets of behavioral functions (Barth et al., 2005;

219   Dadda et al., 2010; Facchin et al., 2009) – including "binary" opposing strategies such as escape

220   and freezing –, whose processing seems to be guaranteed by the asymmetrical structure DHb

221   thought to have evolved under the natural selection pressure resulting from functional

222   incompatibility between these behaviors (Ichijo et al. 2017). In the left dHb, high levels of the

223   potassium channel tetramerization domain-containing protein 12.1 (*kctd12.1/leftover/lov*) are

224   expressed, while low levels are observed in the right dHb. Conversely, two other members of the

225   KTCD family, *kctd12.2* (*right on/ron*) and *kctd8* (*dexter/dex*), are expressed exclusively in the right

226   dHb (Beretta et al., 2012; Gamse et al., 2005; Y. Kuan et al., 2007; Roussigné et al., 2011). High

227   levels of *murcb* and the adrenoceptor beta 2 *adrb2a* are found in clusters enriched in the right dHb,

228   while clusters enriched in the left dHb show high levels of the protochaderin *pcdh7b*, the Wnt

229   family member *wnt7aa*, adenylate cyclase-activating polypeptide *adcyap1a*, and the protein

230   phosphatase regulatory inhibitor *ppp1r1c* (Pandey et al., 2018). These genes have been used as

231   markers for the neuroanatomical divisions of the dHb. However, caution should be exercised in

232   transposing these neuroanatomical subdivisions to functional ones: DeCarvalho et al. (2014)

233   showed that cholinergic neurons in the left dHb are a distinct population from cells expressing

234   *kctd12.1*, and part of the developmental expansion of the lateral dHb from larvae to adults is

235   accompanied by the invasion of the left dHb with cholinergic neurons (in larvae, most neurons in

236   the left dHb are glutamatergic only) and an expansion of substance P and somatostatin-expressing

237   neurons.

238   While the dHb is asymmetric, the ventral habenula (vHb) is symmetric (Amo et al., 2010;

239   Okamoto et al., 2011). The vHb is characterized by the expression of *diamine oxidase* (*dao*), *kiss1*

240   and *protocadherin 10a* (*pcdh10a*) mRNA (Amo et al., 2010; Beretta et al., 2013). Cluster Hb11 is

241   marked by high expression of the transcription factor *sox1a*, cluster Hb12 by high expression of the

242   5-HT$_{1A}$ receptor *htr1aa*, cluster Hb13 by high expression of *beta-tubulin 5* (*tubb5*), and cluster

243   Hb15 by the high expression of the kisspeptin gene *kiss1* (Pandey et al., 2018). Again, these genes

244   have been used as markers for the neuroanatomical subdivision of the vHb.

245   The neuroanatomical asymmetry of the dHb has produced an interesting literature on its

246   behavioral correlates, especially in zebrafish. The neuroanatomical asymmetry correlates with

247   behavioral asymmetries in different assays. Animals with left parapineal position (L-PPO) tend to

248   use their right eye when viewing a mirror and swim preferentially in a clockwise direction, while

249   animals with right parapineal (R-PPO) do not show this preference; conversely, R-PPO zebrafish

250   use the right eye to inspect a live predator, while L-PPO animals show no preference (Taylor et al.,

251   2011). Importantly, while these animals show preference for eye use for a stimulus which elicits

252   aggression (mirror image) or defensive behavior (predator), no eye preference whatsoever is

253   observed towards "neutral" stimuli (Y.-S. Kuan et al., 2007) In addition to the lateralization of

254   behavior, some important differences are observed in adult behavior in other domains. In the first

255   minutes of an open tank test, R-PPO fish show less thigmotaxis than L-PPO fish; likewise, R-PPO

256   fish spend more time near a predator towards the end of the task (Aizawa et al., 2011; Beretta et al.,

257   2012; Concha et al., 2009; Okamoto et al., 2011). In the *frequent-situs-inversus* lineage, larvae with

258   a left-lateralized habenula (LH) begin to view their mirror image with the right eye, but then change

259   to the left eye by the end of a five-minute period; in larvae with a right-lateralized habenula (RH),

260   this pattern is reversed (Dadda et al., 2010; Domenichini et al., 2011). When adults are confronted

261   with a two-choice bead test, *frequent-situs-inversus* lineage fish with a left-lateralized habenula fish

262   (LH *fsi*) bite the right target, while RH *fsi* fish bite the left target. In an emergence test, when LH *fsi*

263   fish are confronted with a black stripe they show progressively increasing latencies to change

264   compartment; while this effect is observed in RH *fsi* fish, it is much smaller (Barth et al., 2005).

265   These results seem to suggest that a right-lateralized habenula decreases responsiveness to novel

266   and threatening stimuli.

267   Contrary to this hypothesis, however, zebrafish expressing the tetanus toxin light chain in

268   the dHbL [Tg(*narp:GAL4VP16*; UAS:TeTxLC) lineage] show more bottom-dwelling in a novel tank,

269   as well as increased freezing responses to an alarm substance combined with the presentation of a

270 moving shadow above the tank (Mathuru and Jesuthasan, 2013); nonetheless, *c-fos* or *egr1*

271 expression is not significantly changed in the dHb after exposure to an alarm substance in zebrafish

272 (DeCarvalho et al., 2013). On the other hand, in larvae, expression of botullin toxin light chain

273 [Tg(*gng8: Gal4*; UAS:BoTxBLC-GFP)] in the dHbL (but not in the dHbR) impairs light preference

274 (Zhang et al., 2017), consistent with decreased anxiety (Steenbergen et al., 2011). Adult animals

275 with silenced dHbL show increased dark preference (Zhang et al., 2017), consistent with *increased*

276 anxiety (Maximino et al., 2010a). Cheng et al. (2017) demonstrated in larval zebrafish habenular

277 responses to light "on" and "off" responses are mediated by the nucleus in the anterior thalamus.

278 This nucleus innervates the dorsal left neuropil of the habenula and converges information about

279 environmental illumination because it receives afferents from the retina and pineal. This thalamo-

280 habenula projection seems to be involved in the ability of blue light to mask circadian variations

281 in behavior (Lin and Jesuthasan, 2017). The role of this thalamo-habenular pathway on light/dark

282 preference, however, is still unknown. Moreover, exposure to the light/dark assay, a model of

283 anxiety-like behavior, increased *cfos* mRNA expression in the dHb of zebrafish, but only if they are

284 handled before the experiment (Lau et al., 2011). A subset of neurons in the dHbL, expressing the

285 myosin phosphatase Rho-interacting protein *mprip*, shows increased *cfos* mRNA expression after an

286 electric shock (Pandey et al., 2018). These results suggest that the zebrafish dHbL is an important

287 center in defensive behavior, being necessary to mount an adaptive response to innate aversive

288 stimuli; in adults, dHbL appears to inhibit anxiety- and fear-like behavior, while in larvae it appears

289 to increase it.

290   Other important pharmacogenetic work attempted to establish the role of the habenula in

291 stimulus appraisal and behavioral control in zebrafish. In the first work, Agetsuma and colleagues

292 (2010) expressed the tetanus toxin light chain [Tg(*narp:GAL4^{VP16}; UAS:TeTxLC*)] or a

293 nitroreductase-mCherry fusion protein in dHbL neurons, and were thus able to block synaptic

294 transmission in that area. When they reached maturity, animals were trained in a cued fear

295   conditioning task; while controls showed increased flight behaviors to the cue after conditioning,

296   dHbL-silenced fish instead showed persistent freezing to the cue. In another experiment, Lee et al.

297   (2010) expressed the photo-sensitizer KillerRed in a ventral telencephalon-habenula projection, and

298   photobleaching on the left habenula led to deficits in the acquisition of two-way avoidance and

299   hyperarousal after light onset before conditioning. They also expressed TeTxLC in the dHbL,

300   obtaining the same result regarding avoidance conditioning deficit.

301   Interestingly, the dHbL has also been implicated in social conflict resolution. Chou et al.

302   (2016) showed that, after the establishment of social dominance, loser (socially submissive) fish

303   show intense activity in the ventral IPN and median raphe and a very reduced responsiveness of the

304   dorsal IPN after acute electrical stimulation of the Hb. These results suggested a participation of

305   different dHb-IPN pathways in the behavioral plasticity that is associated with the losing

306   experience.   Indeed,   zebrafish   expressing   the   tetanus   neurotoxin   in   the   dHbM

307   [Tg*(gpr151:GAL4VP16; brn3a-hsp70:GFP-Cre; UAS:loxP-DsRed-loxP-GFP-TeNT)*]   show   a

308   consistent trend to win fights, while dHbL-silenced [Tg*(narp:GALVP16; UAS:TeNT)*] fish showed a

309   consistent trend to lose fights (Chou et al., 2016). The authors proposed that the reduction in the

310   dHbL-iIPN-GC pathway could switch behavior from offensive behavior to defensive behavior (i.e.,

311   from attacking to fleeing), resulting in losing the fight. Conversely, reduction in the dHbM-vIPN-

312   MRN pathway results in winning the fight by disinhibiting the MRN, which would tend to increase

313   resilience to aversive stimuli.

314   The role of the vHb has been less extensively studied. An interesting exception is the work

315   of Amo et al. (2014), which demonstrated two types of responses in vHb neurons after fear condi-

316   tioning. One type responds phasically to an unconditioned stimulus (US) before conditioning, a re-

317   sponse which is gradually substituted by sustained firing for all duration of the presentation of the

318   conditioned stimulus (CS). A second type responds phasically to the US and gradually substitute

319   this response to phasic firing to the CS. Amo et al. (2014) suggested that these responses code for

320   aversive expectation value and prediction error, respectively. Multi-unit activity of the vHb in-

321   creases in the early stages of active avoidance conditioning and later returns to normal, suggesting

322   that the vHb encodes the negative reward expectation value in active avoidance learning (Amo et

323   al., 2014). Expression of TeTxLC in the vHb abolishes active avoidance learning without alterations

324   in basal anxiety-like behavior or fear conditioning, strengthening the hypothesis of a specific role in

325   active avoidance conditioning; finally, pairing the optogenetic activation of the vHb with a specific

326   tank compartment elicits avoidance of that compartment only when the stimulation is tonic, but not

327   when it is phasic. Overall, these results suggest that tonic responses in the zebrafish vHb represent

328   an aversive expectation value, participating in a larger vEP-vHb-MRN circuit (Amo et al., 2014).

329   Another important evidence for the role of the vHb comes from work with kisspeptin, a sys-

330   tem of peptides associated with reproductive behavior. In zebrafish, the neuropeptide Kiss1 is ex-

331   pressed only in the vHb, while Kiss2 is expressed in the hypothalamus (Servili et al., 2011). These

332   Kiss1-positive co-express glutamate, and project to glutamatergic interneurons in the IPN and MRN

333   (Nathan et al., 2015a). Interestingly, kissr1 receptors are not found in the raphe, but can be found in

334   the vHb and the IPN (Ogawa et al., 2012). Intracranial administration of Kiss1 increases c-Fos ex-

335   pression in the vHb and MRN, and increases the expression of serotonergic system-related genes

336   (*pet1* and *slc6a4a*) (Ogawa et al., 2014, 2012). It is not known whether CAS induces c-Fos expres-

337   sion in the vHb, since DeCarvalho et al. (2013) only reported results from the dHb. Kiss1 also in-

338   duces a dose-dependent effect on vHb neurons, with low concentrations leading to depolarization

339   and high concentrations leading to hyperpolarization (Lupton et al, 2017). Importantly, Kiss1

340   blocks responses to CAS (Ogawa et al., 2014), an effect which is mediated by 5-HT$_{1A}$ and 5-HT$_2$ re-

341   ceptors (Nathan et al., 2015b). Paradoxically, Kiss1 mutant zebrafish with a stop codon upstream of

342   the active peptide show impaired performance in an active avoidance task (Lupton et al., 2017). In-

343   terestingly, Kiss1 mutants also show blunted calcium responses in the superior raphe after an elec-

344   tric shock (Lupton et al., 2017). These results underline a mechanism by which the vHb-MRN cir-

345   cuit works: aversive stimuli activate Kiss1/glutamatergic neurons in the vHb, which project to exci-

346   tatory interneurons in the IPN and raphe. This feed-forward mechanism induces the activation of

347   the raphe, encoding expectations of dangerous outcomes. These expectations can be compared to

348   real outcomes by the activation of 5-HT$_{1A}$ and 5-HT$_2$ receptors, which have been shown to be im-

349   portant in controlling aversive behavior in zebrafish (Maximino et al., 2014, 2013b; Nowicki et al.,

350   2014). Lupton et al. (2017) suggested that this excitatory stage, associated with increased aversive

351   expectation, favors CS-US association, while the next stage in avoidance learning is mediated by

352   kisspeptin-evoked inhibition of the habenula and consequent reduced aversive expectations once the

353   strategy to avoid the US has been learned.

354   There is still little work on the interactions between the dorsal and ventral portions of the

355   habenula in aversive reactions. The different functional roles of these circuits, however, suggest

356   some complementarity. While the ventral aspects appear to be involved in coding aversive value –

357   especially through the vHb-raphe pathway –, the dorsal pathway appears to be involved in shifting

358   behavioral strategies from active to passive coping. It is highly likely that this "switch" function de-

359   pends on information on aversive value and expectations; whether this is provided directly by vHb-

360   dHb connections, or indirectly, by a feedback loop organized by the raphe, is so far unknown.

361   Moreover, this is likely an oversimplification of the role of the habenula in a larger circuit that in-

362   cludes the telencephalon and other portions of the aversive brain system.

363

364   **4. Hypothalamic circuits for defense**

365   The hypothalamus of teleosts fish presents pair of ventrolaterally extending hypothalamic

366   lobes. These lobes ranges from moderately elevated lobes up to hemisphere-like corpora reaching

367   almost the size of the optic tectum (Senn, 1981). The use of diverse model systems to study hypo-

368   thalamus development has provided evidence that the molecular pathways regulating hypothalamic

369   induction and patterning are generally conserved from fish to mammals. In addition, the basic hy-

370   pothalamic cell types and the codes of gene expression that specify them are also highly homolo-

371   gous throughout vertebrate species (Xie and Dorsky, 2017). The fish hypothalamus contains equiva-

372   lents to most if not all of the mammalian hypothalamic cell types. The hypothalamic neurons are all

373   located in stereotypical clusters within the ventral diencephalon hypothalamic and neuronal popula-

374   tions that control the pituitary in fish have been conclusively shown to be functionally analogous to

375   their mammalian counterparts (Machluf et al., 2011).

376   In teleost fish, partial homologies for hypothalamic nuclei that are relevant for defensive

377   behavior have been proposed: the preoptic area (POA), for example, is composed of cells of

378   different sizes that form clusters considered homologous to mammalian hypothalamic nuclei

379   (Goodson and Kingsbury, 2013). Groups of magnocellular and gigantocellular cells are considered

380   homologous to the supraoptic nucleus, while the cluster of parvocellular cells is supposed to be

381   homologous to the paraventricular nucleus (Moore and Lowry, 1998). Between the POA and

382   ventral hypothalamic region there is a transition zone called ventral tuberal region (VTN) that is

383   thought as homologous to the mammalian anterior hypothalamus (AH), and in the ventrocaudal part

384   of the hypothalamus is located the ATN, a putative homolog of the mammalian VMH (Forlano et

385   al., 2005; Forlano and Bass, 2011; Goodson, 2005; O'Connell and Hofmann, 2011). The AH is a

386   source of vasopressin in the mammalian brain, and activation of these vasopressinergic neurons

387   increases aggressive behavior in rodents (Gobrogge et al., 2007).

388   Hodology also supports the homology of these regions. Both the ATN Several

389   hypothalamic regions of teleosts, including ATN and VTN, are connected to the Vs (Folgueira et

390   al., 2004), which has been proposed as homologous to the medial amygdala (Biechl et al., 2017) or

391   to the extended central amygdala (Maximino et al., 2013a) – regions which, as discussed above,

392   participate in the processing of aversive stimuli and defensive responses of both mammals and

393   teleosts. Thus, it is possible that these connections of hypothalamic regions to Vs are related to

394   regulation of defensive behavior in fish.

395   Unfortunately, no functional studies have been made assessing the role of the ATN and

396   VTN in behavioral responses. In teleosts, arginine vasotocin (AVT, the homologue to vasopressin)

397   is also expressed in the VTN (Rodriguez-Santiago et al., 2017), and manipulating AVT levels

398   decreases antipredator behavior in zebrafish (Braida et al., 2012). However, AVT is also expressed

399   in other brain regions, including the POA and pallial and subpallial amygdala (Rodriguez-Santiago

400   et al., 2017), precluding any speculation as to the role of the VTN. The ATN of teleosts also

401   expresses sex steroid hormone receptors, as is the case of the VTN (O'Connell and Hofmann,

402   2012). Stimulation of the ATN elicits reproduction-related vocalizations in male midshipman fish

403   *Porichthys notatus* (Goodson and Bass, 2000), suggesting a role in reproductive behavior; however,

404   a role in defensive behavior has not yet been determined.

405   Indirect evidence for a participation of the hypothalamus in defensive behavior is stronger

406   in relation to neuroendocrine endpoints, especially cortisol responses, given that these responses are

407   under descending hypothalamic control. Aversive stimuli which have been shown to elicit cortisol

408   responses in zebrafish include acute chasing stress (de Abreu et al., 2016; Idalencio et al., 2017;

409   Tran et al., 2014), acute restraint stress (Abreu et al., 2017a; Ghisleni et al., 2012), unpredictable

410   chronic stress (Piato et al., 2011), exposure to the novel tank or the light/dark test (Kysil et al.,

411   2017), and subordinate-dominant interactions (Pavlidis et al., 2011). CAS also elicits increases in

412   cortisol responses in Nile tilapia (Silva et al., 2015) and zebrafish (Abreu et al., 2017a; Schirmer et

413   al., 2013); interestingly, cortisol responses are also observed after visual contact with a predator in

414   zebrafish (Barcellos et al., 2010, 2007), and *D. rerio* also appears to be able to communicate

415   predation risk to conspecifics, since cortisol responses are observed after seeing a shoalmate

416   displaying antipredator behavior (Oliveira et al., 2017, 2013).

417   Presently little is known about either a causal relationship between cortisol and behavioral

418   responses to aversive stimuli in fish, or about which hypothalamic regions are involved in these

419   responses. A clue comes from Ziv et al. (2013) and Griffiths et al. (2012), which used a mutant

420   zebrafish lineage (gr^{s357}) with non-functional glucocorticoid receptors. Larvae from this line show

421   elevated whole-body cortisol levels, increased expression of pro-opiomelanocortin, and no

422   suppression of stress markers after dexamethasone treatment (Griffiths et al., 2012). These larvae

423   also show more auditory-evoked startle responses when compared to wild-type controls, an

424   phenotype that is rescued by treatment with fluoxetine (Griffiths et al., 2012). Adult gr^{s357} animals

425   show abnormal freezing behavior when introduced to a novel tank, reduced exploratory behavior,

426   and lack of habituation to environmental novelty (Ziv et al., 2013); chronic treatment with

427   fluoxetine rescue this phenotype and suppresses the stress-induced upregulation of the

428   mineralocorticoid receptor and the serotonin transporter *scl6a4a* (Ziv et al., 2013). These results

429   suggest a developmental role for the glucocorticoid receptor on shaping the serotonergic system

430   and, as a consequence, increasing anxiety-like behavior in both larvae and adults. The acute effect

431   of cortisol is unknown in this species; in goldfish, cortisol rapidly increases Mauthner cell

432   excitability (Bronson and Preuss, 2017), suggesting an acute, non-genomic mechanism to facilitate

433   the brainstem escape network (see below). Finally, in the crucian carp *Carassius carassius*, the

434   CRF_1 receptor antagonist antalarmin suppresses CAS-elicited responses (Lastein et al., 2008),

435   suggesting a role for CRF in these responses; however, it is not known whether this response is

436   mediated by the hypothalamus or by extra-hypothalamic sites, such as the Dm.

437

5. Tectal circuits for detection of visual threatening stimuli

439   The most prominent structures within the fish tectum are the optic tectum (TO) and torus

440   semicircularis (TS); they are homologous to the mammalian superior and inferior colliculi, respec-

441   tively (Nieuwenhuys et al., 1998). Zebrafish present at least six easily identifiable tectal layers

442   (from superficial to deeper: marginal [MS], optic [SO], superficial fibrous and gray [SFGS], central

443   gray [SGC], central white [SAC], and periventricular strata [SPV]). It has been observed that, in all

444   vertebrates, the upper layers of the tectum are retinorecipient, while the deeper layers house the pro-

445   jection neurons (Butler and Hodos, 2005). In rodents, information from the upper visual field is rep-

446   resented in the medial optic tectum, while information from the lower visual field is represented in

447   the lateral portion; likewise, stimulation of the lateral portion leads to approach-like and appetitive

448   movements, while stimulation of the medial portion leads to defensive-like behavior (Brandão et al.,

449   2003, 1999). In rodents, these medial regions receive exclusive projections from multimodal and as-

450   sociation sensory cortices, visual thalami, hypothalamic nuclei associated with defensive behavior,

451   and a few pretectal nuclei (Comoli et al., 2012). In goldfish, the medial tectal zone seems to be re-

452   lated to orienting responses, the anteromedial zone to goal-directed saccades, the extreme anterome-

453   dial zone to eye convergence, and the posterior zone to escape responses (Herrero et al., 1998; Salas

454   et al., 1997).

455   Many different interneurons have been described in the OT (Figure 2A). Superficial in-

456   terneurons (SINs) in the superficial layers (SO and SFGS) are GABAergic (Scott and Baier, 2009).

457   About 75% of the cells from the periventricular stratum (SPV) are GABAergic, while 10% are glu-

458   tamatergic (Nevin et al., 2010; Robles et al., 2011). Glutamatergic cells from the tectum are of the

459   bistratified periventricular (bsPVIN) interneuron type, with somata which locate in the deeper and

460   intermediate regions of the SPV, a single apical process that spans the SGC and SFGS, and gluta-

461   matergic axons which terminate in the layer between both of these strata (Nevin et al., 2010; Robles

462   et al., 2011). Another group of cells, the non-stratified periventricular (nsPVIN) type, is a small

463   population of GABAergic interneurons located deep in the SPV, arbor in the deeper regions of the

464   SGC and SFGS; they lack the stratification and laminar specificity of bsPVIN cells, with their ax-

465   ons terminating mostly in the SGC and in between this stratum and the overlying SFGS and the un-

466   derlying SAC (Nevin et al., 2010; Robles et al., 2011; Scott and Baier, 2009). Finally, periventricu-

467   lar projection neurons (PVPNs) are GABAergic cells with a dendritic arbor spanning the regions

468   between SFGS and SGC, the SGC itself, and the region between SGC and SAC, and an axon that

469   forms a sparse arbor of collaterals in the vicinity of the lateral longitudinal fascicle and the hind-

470   brain escape network (Nevin et al., 2010; Robles et al., 2011; Scott and Baier, 2009). Some periven-

471   tricular projection cells course medially and terminate in the superior raphe (Nevin et al., 2010), but

472   it is not known whether these cells are GABAergic or not; however, lipophilic dye injection into the

473   tectal neuropil marks a much larger population of axons than the GABAergic neurons, suggesting

474   that this is a small and very specialized projection (Nevin et al., 2010; Scott and Baier, 2009).
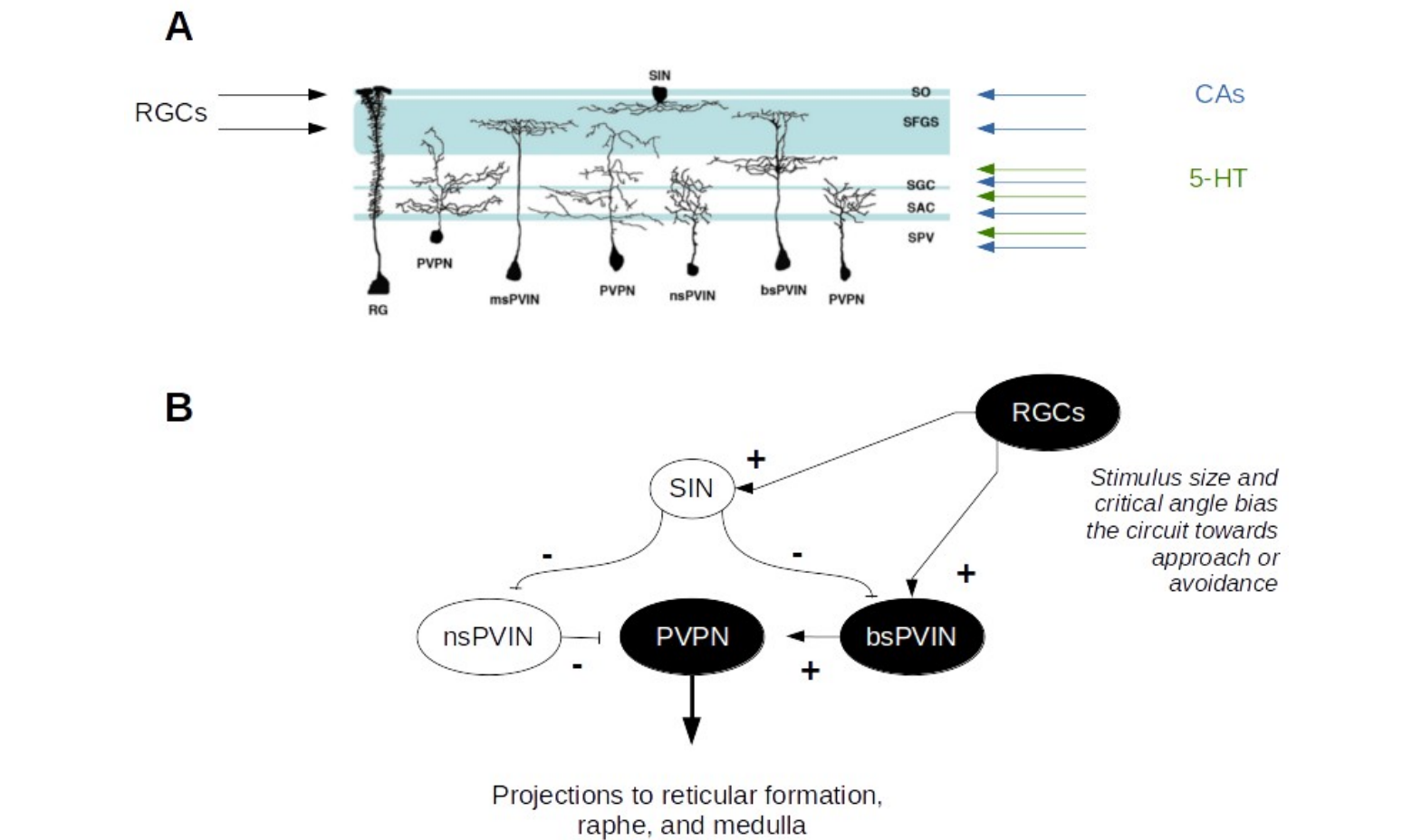
Figure 2: (A) Depiction of the tectal interneurons that participate in the escape circuit. The upper layers of the tectum (stratum opticum and stratum fibrosum et griseum superficiale) are retinorecipient, and also receive catecholaminergic (CAs) projections. Interneurons in the deeper layers (stratum griseum centrale, stratum album centrale, stratum periventriculare) participate in decision-making, and receive serotonergic (5-HT) and catecholaminergic projections. Identified interneuron types include the superficial inhibitory interneuron (SIN), as well as a variety of periventricular interneurons (non-stratified [nsPVIN], bistratified [bsPVIN], and mono-stratified [msPVIN] interneurons). Morphologically distinct periventricular projection neurons (PVPNs) have also been identified. (B) Stimulus properties, including size, are coded by retinal ganglion cells (RGCs) bias the circuit towards approach (smaller size) or avoidance (large size). (B) These stimuli activate inhibitory SINs and excitatory bsPVINs. SINs also fine-tune responses of bsPVINs, and disinhibit PVPNs by inhibiting nsPVINs. These projection neurons, in its turn, modulate the activity of the reticular formation, raphe, and medulla.

476   bsPVINs, nsPVINs and PVPNs have been thought of as representing different parts of a cir-

477   cuit for detecting visual threats and selecting appropriate responses (Fig. 2B). The distribution of

478   the neuropil, as well as the glutamatergic nature of the bsPVIN neuron type suggest that these cells

479   perform superficial to deep information transfer (Nevin et al., 2010; Robles et al., 2011). In con-

480   trast, the inhibitory nsPVIN is a GABAergic interneuron, producing feed-forward inhibition to filter

481   the visual information transmitted onto projection neurons (Robles et al., 2011). Moreover, the loca-

482   tion of their dendrites primarily in the SGC layer, which receives non-visual afferents from the te-

483   lencephalon and thalamus, suggest that they might integrate inputs from visual and non-visual areas

484   (Nevin et al., 2010). Since projection cells from the tectum have dendrites in the deeper and inter-

485   mediate layers of neuropil (but not the superficial layers), this suggests that they are not directly

486   retinorecipient (Butler and Hodos, 2005), and therefore must receive information from bsPVIN and

487   nsPVIN cells.

488   In zebrafish, the role of these circuits in escape responses has been described in a series of

489   elegant experiments in larvae. Zebrafish larvae respond to a moving dot stimulus in a size-depen-

490   dent way: if the stimulus is relatively small (e.g. potential prey), the animal approaches it, while

491   larger stimuli (e.g., potential predators) are avoided (Barker and Baier, 2015). Silencing tectal neu-

492   rons completely abolishes both approach and avoidance responses, irrespective of stimulus size.

493   When SINs are ablated, however, large object avoidance is impaired (Barker and Baier, 2015). In-

494   terestingly, ablating tectal cells marked in the *Gal4mpn354* line – most of which are glutamatergic

495   nsPVINs – shift behavior from approach to avoidance, with ablated larvae avoiding small stimuli;

496   optogenetic stimulation of these neurons produce the opposite effect (Barker and Baier, 2015).

497   Noteworthy, larvae acutely treated with fluoxetine, therefore increasing serotonergic tone, decrease

498   the probability of avoiding small and medium stimuli, but do not affect responses to larger stimuli

499   (Filosa et al., 2016), suggesting that this neurotransmitter does not participate in the control of es-

500   cape responses by the OT, but instead participates in shifting from fleeing to foraging.

501   Using a different stimulus – a "looming" dot that increases in size, simulating a predator

502   strike – it was demonstrated that zebrafish larvae attempt to escape this stimulus (Dunn et al., 2016;

503   Temizer et al., 2015), and that this stimulus activates three specific targets of retinal ganglion cells:

504   arborization fields AF6 and AF8, and the OT (Dunn et al., 2016; Temizer et al., 2015). In the OT,

505   responses were observed in the SFGS and SGS (Temizer et al., 2015); a specific response is ob-

506   served in SINs (Dunn et al., 2016). It appears that these SINs modulate the inputs from retinal gan-

507   glion cells to periventicular projection neurons, "fine-tuning" the motor command produced by

508   these later cells to critical angle (Dunn et al., 2016). The higher density of looming-selective re-

509   sponses in the OT in relation to extra-tectal retinorecipient areas suggest that the OT is involved in

510   processing looming stimuli, while AF6 and AF8 process other visual cues such as whole-field mo-

511   tion and luminance changes. Indeed, ablation of retinotectal projections – leaving intact projections

512   to other AFs – impaired the ability of larvae to escape the looming stimulus (Temizer et al., 2015).

513   Ablation of the brainstem escape network – one important motor output from OT – resulted in a

514   specific bend deficit in response to looming stimuli, suggesting a participation of these neurons in

515   the escape response elicited by looming stimuli (Dunn et al., 2016).

516

6. The brainstem escape network

518   The concept of a "brainstem escape network" was introduced to describe gigantocellular

519   neurons in the brainstem of fish (the Mauthner [M-]cells, its two segmental homologs MiD2cm and

520   MiD3cm, and other identified neurons in the reticulospinal segments adjacent to the Mauthner cells)

521   that activate fast-start responses that are used by fish to escape predatory attacks (Eaton et al.,

522   2001). These reticulospinal system receives massive primary acoustic input as well as sensory in-

523   puts from the optic tectum, and synapses on motoneurons that innervate trunk muscle on the con-

524   tralateral side (Kinkhabwala et al., 2010). The activation of M-cells produces a robust turn of about

525   45º, leading to the initiation of a very fast response called C-start (Furukawa and Furshpan, 1963;

526   Eaton et al., 1977) that is fine-tuned to the angle of stimulation; the participation of the other com-

527   ponents of the brainstem escape network code other kinematic features that result in propelling the

528   fish away from the stimulus (Eaton et al., 2001). These responses are very fast; in zebrafish, the la-

529   tency for a C-start after acoustic stimulation was recorded as about 5 ms (Eaton et al., 1977), and

530   the latency for looming visual stimuli varied from 10-20 ms (Temizer et al., 2015) to a few hun-

531   dreds of milliseconds (Dunn et al., 2016).

532   The brainstem escape network receives inputs from many different regions of the teleostean

533   brain. As described, escape responses to visual stimuli are mediated by the optic tectum (Dunn et

534   al., 2016; Temizer et al., 2015), which projects to this system. While telencephalic projections have

535   not yet been described, telencephalic ablation decreases startle probability in goldfish (Collins and

536   Waldeck, 2006), suggesting a facilitatory role; whether this is due to ablation of pallial or subpallial

537   amygdalar components is unkown.

538   Monoaminergic inputs are also important in the modulation of C-starts. In zebrafish larvae,

539   tyrosine hydroxylase and 5-HT immunoreactivity was observed closely apposed to the ventral den-

540   drites of the M-cell, MiD2cm, and MiD3cm, and tyrosine hydroxylase immunoreactivty was ob-

541   served near the lateral dendrite (McLean and Fetcho, 2004). 5-HT increases inhibitory currents pro-

542   duced by activation of presynaptic pathways, while dopamine increases the amplitudes of electrical

543   and glutamatergic components of auditorily evoked responses (Korn and Faber, 2005).

544   While this apparently simple reflex has been considered to be a "fixed action pattern", with

545   little modulation by upstream structures and therefore little relevance for fear- and anxiety-like

546   states, there is interesting evidence for considerable plasticity of this system (Medan and Preuss,

547   2014). Larval zebrafish present prepulse inhibition (PPI), in which the probability of a C-start is re-

548   duced when it is preceded by a non-startling sound (Burgess and Granato, 2007). This prepulse

549   sound attenuates the synaptic response of M-cells to a subsequent auditory stimulus (Curtin et al.,

550   2013; Medan and Preuss, 2014, 2011). In zebrafish, the PPI is disrupted by apomorphine, a

551   dopaminergic agonist (Burgess and Granato, 2007); in goldfish, apomorphine blocks the prepulse

552   sound-evoked reduction in M-cell membrane resistance (Medan and Preuss, 2011; Neumeister et

553   al., 2008).

554   5-HT has been implicated in social modulation of startle responses in the African cichlid

555   *Astalotilapia burtoni* (Whitaker et al., 2011). In this species, dominant males show increased startle

556   probability and lower escape thresholds when compared to subordinate males (Neumeister et al.,

557   2010), perhaps as a compensation of the increased conspicuity caused by brighter body coloration

558   and higher activity (Medan and Preuss, 2014; Neumeister et al., 2010). The behavioral increases in

559   startle are accompanied by increased excitability of M-cells to auditory stimuli, as well as a reduc-

560   tion on the inhibitory drive (Neumeister et al., 2010). The 5-HT$_2$ receptor antagonist ketanserin de-

561   creases feedback inhibition in subordinate, but not dominant, African cichlids (Whitaker et al.,

562   2011). These represent presynaptic mechanisms, since only 5-HT$_{5A}$ and 5-HT$_6$ receptors are ex-

563   pressed in Mauthner cells (Whitaker et al., 2011).

564

565   **7. Conclusions**

566   Different regions from the rostrocaudal axis appear to be involved in detecting, identifying,

567   processing, and responding to aversive stimuli in fish. In general, threats are detected and processed

568   at the level of the Dm, which may also be responsible for response selection at certain situations.

569   This region is homologous to the mammalian frontotemporal amygalar cluster (Maximino et al.,

570   2013a). The "classical model" of the role of the amygdala in fear involves aversive learning in the

571   frontotemporal amygdala, while the behavioral output would be mediated by the autonomic/limbic

572   amygdala (Vargas et al., 2012). Recent evidence, however, suggests that the frontotemporal amyg-

573   dala is involved in encoding emotional events (including aversive stimuli and contexts) with refer-

574   ence to particular sensory features, while the autonomic amygdala encodes the motivational or af-

575 fective significance (Balleine and Killcross, 2006). This is consistent with our hypothesis that the

576 Dm also is responsible for mounting appropriate coping (active vs. passive) responses.

577   A parallel circuit for negative incentive and coping has been described in the habenula as

578 well. The vHb appears to represent aversive expectation values and modulate aversive behavior via

579 the median raphe nucleus (Amo et al., 2014). Similarly, a dHBM-vIPN-MRN appears to be involved

580 in resilience to aversive stimuli and/or active coping, while the dHBL-iIPN-GC appears to be in-

581 volved in selecting appropriate responses (Okamoto et al., 2011). So far, it is not known if this cir-

582 cuit is parallel to the (more classical) amygdalar/Dm one, or whether there are neuroanatomical

583 connections between Hb nuclei and Dm and/or Vs, but an indirect projection to the vHb via the ven-

584 tral entopeduncular nucleus has been described (Lal et al., 2018). Differently from the disinhibitory

585 Dm-Vs circuit, however, the Dm-vEN-vHb circuit is excitatory. It is possible that both circuits run

586 in parallel and compete (or collaborate) to decision-making in the GC.

587   The participation of these pathways needs to be interpreted in the context of a wider modu-

588 lation of overall brain state, given the relationships between these circuits and downstream neuro-

589 modulators, such as dopamine and serotonin. In the case of the habenular circuit, this is more clear,

590 since both the dHb and the vHb appear to produce their effects by modulating activity in the raphe;

591 as a result, modifying serotonergic phasic and tonic responses in projections from the raphe. How-

592 ever, extensive serotonergic projections have been described to the telencephalon of zebrafish, with

593 important projections to the Dm and Vs/Vp (Lillesaar et al., 2009). Therefore, it is highly likely that

594 not only do neuromodulators such as monoamines act as mediators in the responses, but these trans-

595 mitters also provide important feedback to the more rostral regions involved in threat detection and

596 response selection (Figure 1B)

597   In addition to this "slow" pathways (the "forebrain circuit"), a "quick-and-dirty" pathway

598 for visual aversive stimuli is organized in the optic tectum (the "midbrain circuit")(Carr, 2015). This

599 midbrain circuit is sensitive to stimulus size and critical angle, and switches from approach (small

600 stimuli probably mean "food") to avoidance (large stimuli arriving at a specific angle probably

601 mean "predator strike"). This circuit projects to motor regions of the medulla and spinal cord, as

602 well as to the GC, initiating and/or modulating escape responses that are highly stereotypical. More-

603 over, a putative indirect OT-Dm projection, via the lateral preglomerular nucleus, has been pro-

604 posed in fish as an analogue of the superior colliculus-pulvinar-amygdala pathway of mammals

605 (Carr, 2015). It is expected that visually threatening stimuli activate the first circuit and bypass the

606 Hb-IPN/raphe-GC or the Dm-Vs-GC circuits. Very little is known about the GC of zebrafish – con-

607 trary to the great importance that is given to the periaqueductal gray of mammals as a hub for defen-

608 sive behavior (see Motta et al., 2017, for a recent review) –, an interesting research opportunity to

609 clarify these circuits.

610   The forebrain circuit is functionally similar to LeDoux's (1998, 2000) concept of a "high

611 road", providing slower but highly processed sensory information with affective tones, while the

612 midbrain circuit would be functionally similar to the "low road". In both the proposed forebrain cir-

613 cuit and the "high road", threatening stimuli pass through increased processing of the nature of the

614 sensory stimuli to reach a more precise identification; however, in LeDoux's original formulation

615 the high road refers to cortical processing of sensory information before reaching the amygdala,

616 while the low road refers to information that is sent directly from the thalamus to the amygdala. Not

617 only is the isocortex not the main target of sensory thalamic projections in zebrafish, the participa-

618 tion of putative homologues in aversive behavior has not been established (but see Aoki et al.,

619 2013). Indeed, Carr (2015) suggested that a "high road" is absent in fish, which would only possess

620 a "low road". The present review, however, suggest that some granularity in this interpretation is

621 necessary, given that a differentiation between responses mediated by the forebrain and midbrain

622 circuits is possible.

623   The participation of the habenular pathways in neurovegetative responses is also less clear,

624 but a amygdalar-hypothalamic circuit has been suggested on the basis of c-Fos and p-ERK activity

625 (Faustino et al., 2017; Randlett et al., 2015). Aversive stimuli, including CAS and physical stres-

626 sors, induce cortisol (Abreu et al., 2017b; Schirmer et al., 2013) and norepinephrine and epineph-

627 rine release (Maximino et al., 2014). This is consistent with a classical model of amygdalar control

628 of fear in rodents, in which CEXA-hypothalamic projections regulate the neurovegetative responses

629 to threats (Misslin, 2003). Based on coherence analysis of c-Fos expression to CAS (Faustino et al.,

630 2017), it is suggested that the Dm activates inhibitory Vs neurons, disinhibiting downstream hy-

631 pothalamic mechanisms.

632   What is the "switch" that regulates active vs. passive coping? What conditions favor switch-

633 ing from the forebrain to the midbrain circuits? While the neural bases of these changes are

634 presently unknown, environmental characteristics which lead to decision-making have been de-

635 scribed thoroughly. For example, threat probability and distance vary in a continuum that restricts

636 attention (Andersen et al., 2016), and therefore whether fast or slower responses are needed (Brown

637 et al., 1999; Fanselow and Lester, 1988; Kavaliers and Choleris, 2001; Laundré et al., 2010; Mc-

638 Naughton and Corr, 2004; Perusini and Fanselow, 2015). Thus, decision-making is biased towards

639 escape (flight) or fight responses when the threat is proximal, while avoidance and freezing are

640 elicited when threat is distal (Fanselow and Lester, 1988; McNaughton and Corr, 2004; Perusini and

641 Fanselow, 2015). Similarly, the decision to freeze or flee is dependent on environmental affor-

642 dances, such as the availability of escape routes (Blanchard and Blanchard, 1988). It has been sug-

643 gested that habenular circuits act as comparators for these stimuli, biasing the organism towards

644 careful approach or escape (Okamoto et al., 2011). An exciting possibility is that habenular circuits

645 produce this effect by modulating the activity of serotonergic projections to the Dm and/or Vs and

646 to the OT. This hypothesis is consistent with the Deakin/Graeff hypothesis for the role of serotonin

647 in switching responses from escape towards risk assessment (Deakin and Graeff, 1991; Graeff et al.,

648 1997; Maximino, 2012).

649   Much work is still needed to identify the regions that are responsible for aversive behavior

650 in fish. The present review suggests some of the regions involved and presents a roadmap and

651 framework for future research. The evolutionary relevance is clear, but it is also important to con-

652 sider the implications of these findings for work in the field of behavioral models and experimental

653 psychopathology: establishing homologies between regions involved in similar behavior strength-

654 ens the hypotheses that these behaviors are indeed conserved, an assumption of most models that is

655 rarely tested (Maximino et al., 2010b) and of which depends the construct validity of these models.

656 This implication opens up novel avenues for future research which ought to be prolific.

657

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