The neuromodulatory transmitter serotonin (5-hydroxytryptamine, 5-HT) is synthesized by neurons located in the brainstem, which project more or less densely to the entire central nervous system (Charnay and Leger, 2010). Serotonin regulates a variety of physiological functions, including food intake, reward, reproduction, sleep-wake cycle, memory, cognition, emotion, and mood (Charnay and Leger, 2010). Consistently, dysfunctions of the serotonergic system are involved in the development or progression of mental disorders including autism, insomnia, anxiety, depression, schizophrenia, Parkinson’s disease, or Alzheimer’s disease (Charnay and Leger, 2010). Many of these diseases (e.g., autism, schizophrenia, depression, Parkinson’s disease, Alzheimer’s disease) present with concomitant impairment of olfaction (and memory), often accompanied by a reduced volume of the olfactory bulb (OB; Figure 1A) and hippocampus. These functional impairments may result from distorted adult neurogenesis in the respective neurogenic niches, as OB and hippocampal dentate gyrus are the two major areas of the adult mammalian brain where adult-born cells are generated throughout life. A wide range of studies documents the involvement of adult-born cells in short- and long-term olfactory memory; perceptual, associative, and fear learning, etc. (summarized in Lepouzes et al., 2015; Fomin-Thunemann et al., 2020).

Interestingly, adult neurogenesis and olfactory memory are positively modulated by fluoxetine, an antidepressant drug and selective serotonin reuptake inhibitor (Siopi et al., 2016). Cumulative evidence points towards a specific role for serotonin in adult neurogenesis, as it has been shown that serotonin modulates the fate and functional state of adult-born cells throughout the entire life. Serotonergic projections innervate both the hippocampus and OB (Charnay and Leger, 2010), as well as their respective neurogenic niches, the subgranular zone and subventricular zone (SVZ) (Soumier et al., 2010; Garcia-Gonzalez et al., 2017). Serotonergic fibers innervating the OB originate from the dorsal and medial raphe nuclei and primarily innervate the superficial glomerular layer of the OB (Figure 1B and C), with sparser innervation of granule and mitral cell layers (Petzold et al., 2009; Fletcher and Chen, 2010).

Interestingly, the serotonergic innervation of the glomerular layer of the bulb is not homogeneous, as the density and thickness of innervating serotonergic fibers vary between adjacent glomeruli. Within the neurogenic niche in the SVZ, serotonergic inputs run along the wall of the lateral ventricle (Tong et al., 2014). Here, the radial glia-like cells (B cells) give rise to transient amplifying cells (C cells), which then generate neuroblasts (Figure 1C). Serotonin promotes the proliferation of B and C cells in the SVZ (Brezun and Daszuta, 1999; Soumier et al., 2010; Tong et al., 2014). The thymidine analog bromodeoxyuridine (BrdU) is often used for identification of newborn cells, as it incorporates into the DNA of dividing cells and can later be visualized using immunohistochemistry. Lesioning serotonergic terminals or inhibition of serotonin synthesis leads to a substantial decrease in the number of BrdU-positive (BrdU) adult-born cells in the SVZ (Brezun and Daszuta, 1999), while an infusion of the serotonin-releasing drug fenfluramine into the lateral ventricle of adult mice significantly increases the number of BrdU+ adult-born cells and doublecortin-positive neuroblasts in the SVZ (Tong et al., 2014). Consistently, 5-HT1A and 5-HT2C receptor agonists increased, while 5-HT2C receptor antagonists decreased cell proliferation in the SVZ of adult mice (Tong et al., 2014). Besides, serotonin application induced depolarising inward currents in B cells, which were partially blocked by 5-HT2C or 5-HT5A receptor antagonists. The co-application of 5-HT2C and 5-HT5A receptor antagonists completely abolished serotonin-induced currents in B cells (Tong et al., 2014).

Collectively, these data highlight the importance of serotonin in controlling proliferation and neurogenesis in the SVZ. After leaving the SVZ, adult-born cells - called neuroblasts at this developmental stage - migrate along the RMS towards the OB (Figure 1B and C). Migrating neuroblasts express Ca²⁺-permeable 5-HT3A receptors and serotonergic fibers, projecting along the RMS, have been shown to control velocity and directionality of neuroblast migration in a Ca²⁺-dependent manner (Garcia-Gonzalez et al., 2017). Moreover, a constitutive 5-HT3A receptor knockout presented with thinner RMS, smaller OB, and reduced density of parvalbumin- and calretinin-positive interneurons in the granule cell and the external plexiform layers (see Figure 1C for a schematic illustration of the OB layers).

Upon arrival in the OB, neuroblasts change from tangential to radial migration (Figure 1B and C) and move towards the OB surface to become GABAergic interneurons in the granule or glomerular cell layers. Ninety percent of these cells become granule cells, while 5–10% migrate into the glomerular layer to become periglomerular or to a lesser extent short axon cells (Lepouzes et al., 2015). The latter are collectively referred to as juxtaglomerular cells (JGCs). During the pre-integration phase, i.e.

![Figure 1](image-url)
after arrival to the glomerular layer but before the integration into the local circuit (Liang et al., 2016), functional properties of adult-born JGCs differ from those of resident cells. Thus, adult-born JGCs show lower spontaneous ongoing activity, higher odor sensitivity, greater responsiveness to a larger number of odorants, and increased structural plasticity. When adult-born JGCs mature (approximately at 7–8 weeks after birth), their spontaneous and odor-evoked activities and structural plasticity become more similar to those of resident juxtaglomerular cells (Fomin-Thunemann et al., 2020). However, many adult-born cells do not survive the maturation process and undergo apoptosis 15–45 days after their birth. Interestingly, daily treatment with the selective 5-HT1A receptor agonist 8-hydroxy-2-(di-n-propylaminotetralin significantly increased BrdU cell survival in the dentate gyrus of the hippocampus while the same treatment decreased survival of BrdU granule cells in the OB (Soumier et al., 2010).

Taken together, these observations suggest that state from the beginning of the respective neurogenic niche and until their full maturation, the development of adult-born hippocampal and OB interneurons is controlled by the serotonergic inputs.

But do adult-born cells preserve their privileged serotonergic inputs beyond their maturation, i.e. at times, when their functional properties are supposed to align with those of surrounding resident cells? Our data obtained in mature adult-born JGCs (Fomin-Thunemann et al., 2020) suggest that this might be the case: after application of the nonselective 5-HT2/S-HT7 receptor antagonist methysergide onto the OB surface of awake mice, we observed a significant and selective decrease in the ongoing activity of mature (> 8 week-old) adult-born JGCs. Surprisingly, the same treatment did not influence resident cells. This suggests that despite their abundance in the glomerular layer, serotonergic fibers preferentially target adult-born cells. What could be the functional role of this privileged connection?

Serotonergic projections to the OB were shown to play a key role in selective filtering or attenuation of sensory inputs. Indeed, inhibition of serotonin receptors in general, and 5-HT2C receptors in particular enhanced odor-evoked responses in axons of olfactory sensory neurons projecting from the nose to OB glomeruli, whereas activation of 5-HT2C receptors inhibited these responses (Petzold et al., 2009).

This effect was shown to be mediated through presynaptic GABAergic inhibitory interneurons, which exerted a more pronounced inhibitory effect on the JGCs than did the direct serotonergic inputs (Petzold et al., 2009). Interestingly, many adult-born cells did not survive this treatment and underwent apoptosis, indicating that the survival of adult-born cells might be mediated by the selective 5-HT1A receptor agonist 8-hydroxy-2-(di-n-propylaminotetralin). These findings suggest that the survival of adult-born cells is influenced by the selective 5-HT1A receptor agonist 8-hydroxy-2-(di-n-propylaminotetralin).

In conclusion, serotonergic inputs support major steps of adult neurogenesis in both neurogenic niches of the mammalian brain, including cell proliferation, migration, and survival. Moreover, even after full integration of adult-born cells into the surrounding neural circuitry and maturation therein, serotonergic inputs convey unique functional properties to adult-born cells, enabling them to play a distinctive role in integrating environmental stimuli in a brain state-specific manner.

The present work was supported by the German Research Foundation (DFG) grant GA 654/14-1 to OG.

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