Ultra-high field imaging of the amygdala – A review

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Abstract

The amygdala is an evolutionarily conserved core structure in emotion processing and one of the key regions of interest in affective neuroscience. Results of neuroimaging studies focusing on the amygdala are, however, often heterogeneous since it is composed of functionally and neuroanatomically distinct subnuclei. Fortunately, ultra-high-field imaging offers several advances for amygdala research, most importantly more accurate representation of functional and structural properties of subnuclei and their connectivity. Most clinical studies using ultra-high-field imaging focused on major depression, suggesting either overall rightward amygdala atrophy or distinct bilateral patterns of subnuclear atrophy and hypertrophy. Other pathologies are only sparsely covered. Connectivity analyses identified widespread networks for learning and memory, stimulus processing, cognition, and social processes. They provide evidence for distinct roles of the central, basal, and basolateral nucleus, and the extended amygdala in fear and emotion processing. Amid largely sparse and ambiguous evidence, we propose theoretical and methodological considerations that will guide ultra-high-field imaging in comprehensive investigations to help disentangle the ambiguity of the amygdala's function, structure, connectivity, and clinical relevance.

Keywords: amygdala; neuroimaging; 7T; ultra-high field imaging; fear processing; anxiety

1. Introduction

The amygdala is a subcortical structure located bilaterally in the medial temporal lobes. It plays a crucial role in processing emotional information, especially fear, and social stimuli (Güntürkün, 2019). The amygdala's importance for fear processing is evident in patients with the heritable Urbach-Wiethe's syndrome (Urbach and Wiethe, 1929). In this condition, following the calcification of intraamygdalar blood vessels, patients are unable to recognize and express fear while other emotions remained relatively intact (Adolphs et al., 1994; Feinstein et al., 2011). Furthermore, affected patients have difficulties with appropriate assessment and behavior in social situations and decisions under risk or ambiguity (Adolphs et al., 1998; Brand et al., 2007).

The amygdala is relevant for several neurological and psychopathological disorders. Based on neuroimaging studies, it is assumed that the amygdala plays a role in major depression disorder (MDD; Rubinow et al., 2016). Structural and functional anomalies have also been found in bipolar affective disorder (Garrett & Chang, 2008), anxiety disorders (Rauch et al., 2003), schizophrenia (Aleman and Kahn, 2005), epilepsy, and Alzheimer's disease (Benarroch, 2015). However, results on the amygdala's involvement in psychopathology are ambiguous. For instance, in a 2008 meta-analysis of 13 studies, Hamilton et al. found increased amygdala volumes in medicated patients and decreased amygdala volumes in non-medicated patients with MDD. In a review article, Besteher, Gaser, & Nenadić (2020) identified 16 studies on brain structure and subclinical depression, of which only one found a relationship between amygdala structure and depression. However, they identified six studies that reported either positive or negative correlations between the whole amygdala volume and subclinical anxiety, only one of which attributed the activity to a specific subnucleus of the amygdala, i.e., the basal nucleus (Iidaka et al., 2006).

The core issue in neuropsychiatric amygdala research is that it is not a unified structure but is composed of at least 13 functionally and structurally distinct subnuclei (Pabba, 2013). Some researchers even distinguish between as many as 17 subnuclei in the rat amygdala (McDonald and Mott, 2017). The comprehensive cellular-resolution atlas by Ding et al. (2016) describes 15 subnuclei in the human amygdala (see Figure 1). Table 1 shows the functions of each nucleus.

Insert Table 1 here

These subnuclei are commonly summarized into two distinct groups: the basolateral and centro-medial nuclei (LeDoux, 2007). Other authors suggest categorizing it into a lateral, basolateral, medial, and central nuclei complex (Janak and Tye, 2015). Previous research demonstrated that the nuclei and their substructures serve different purposes. The lateral nucleus, for example, has been shown to serve as the main input center for afferences from the thalamus and cortex and plays an important role in the integration of stimuli in fear conditioning (Güntürkün, 2019; LeDoux, 1993; LeDoux and Muller, 1997). Plasticity in the basolateral amygdala is thought to be involved in the implicit formation of the emotional component of memories during fear conditioning (Fanselow and Ledoux, 1999). The central nucleus is crucial in pain processing as it receives nociceptive input from the parabrachial nucleus (Allen, Bobnar, & Kolber, 2021) and sends efferent signals to the nucleus basalis Meynert in threatening situations (Güntürkün, 2019).

Insert Figure 1 here (use color in print)

Figure 1. Schematic illustration of the subnuclei of the left human amygdala. From left to right, the amygdala is shown in an anterior, medial, and posterior frontal section, viewed from an anterior perspective. White areas show undescribed amygdala matter. AA = anterior amygdala area; AB = accessory basal (or basomedial) nucleus; ACTA = amygdalocortical transition area; AHA = amygdalohippocampal area; AHTA = amygdalohippocampal transition area; ASTA = amygdalostriatal transition area; BA = basal nucleus; Ce = central nucleus; Co = cortical nucleus; En = endopiriform nucleus; INA = intercalated nuclei; IMG = intramedullary gray of the amygdala; LA = lateral nucleus; Me = medial nucleus; PL = paralaminar nucleus. Based on the cellular-resolution atlas by Ding et al. (2016).

The present narrative review aims to provide an overview of the current state of ultra-high-field imaging research of the amygdala to foster a more comprehensive understanding of amygdala function than can be achieved based on the heterogenous results of imaging studies with lower magnetic field strengths. As described above, the amygdala's subnuclei are differentially involved in diverse brain functions. Thus, after an introduction to ultra-high field imaging, we review the literature on amygdala functions. Since the subnuclear functional heterogeneity of the amygdala is inseparably linked to heterogeneity in connectivity, we then investigate the present literature on the structural and functional connectivity on the subnuclear level. After a description of these physiological foundations, we subsequently provide a synthesis of clinical ultra-high field amygdala studies.

2. Advances in high-field imaging: Benefits for amygdala research

Typically, the properties of the human amygdala are investigated using functional or structural magnetic resonance imaging. Most studies apply magnetic field strengths between 1.5 T (Tesla) (Cheng et al., 2003; Orihashi et al., 2020; Wright et al., 2008) and 3 T (Gryglewski et al., 2019; Kraff et al., 2015; Wen et al., 2022). While this method is economical and convenient, these studies often fail to identify small substructures of the amygdala and adjacent areas due to their low spatial resolution (Faull et al., 2015). Traditionally, structural images are acquired at 1 mm isotropic or higher, while for fMRI, resolutions between 2 and as low as 4 mm isotropic are used. Diffusion MRI is often recorded with a resolution of 2-2.5 mm isotropic. In contrast, 7 T imaging enables data acquisition with higher resolutions, (Glasser et al., 2016).

Beside minimal information on the subnuclei of the amygdala, conventional functional neuroimaging is often vulnerable to interferences from visceral activation in ventral brain regions (Sladky et al., 2018, 2013). Therefore, ultra-high field imaging is needed to overcome these deficits and to enable detailed research on small brain structures. The increased contrasts and higher temporal and spatial resolution of 7 T imaging allow for more reliable measures on the submillimeter level due to smaller voxels (usually between 0.3 mm and 1.0 mm isotropic; Keuken et al., 2018). Moreover, with higher spatial resolution, field-inhomogeneities can be recorded more sensitively. The combination with nuisance regressors enables canceling out strong temporal signal fluctuations in ventral regions of interest. Due to high contrast, details on the submillimeter level can be easily visualized, allowing for more reliable discrimination of subnuclear structures (Sladky et al., 2013). Ultra-high field imaging is currently used to investigate fear extinction (Batsikadze et al., 2022), addiction (Brand et

al., 2016), and neuroendocrinology (Thielen et al., 2019), and is discussed as a promising tool for tumor localization (Patel et al., 2020).

The most frequently used ultra-high field strength is 7 Tesla, enabling investigations of voxel sizes up to 0.2 x 0.2 x 0.2 mm (Siemens Healthcare GmbH, 2022). Structural investigations mostly use T1-weighted MP2RAGE sequences with isotropic 0.7 mm to 0.9 mm voxels, while functional scans were preferably conducted using T2-weighted FLAIR or EPI sequences with a spatial resolution between 0.47 x 0.47 x 3 mm and isotropic 1.5 mm voxels. Since the amygdala is parcellated in subnuclei less than a millimeter in diameter, ultra-high field imaging seems obligatory for the reliable investigation of these substructures. In the following sections, we will briefly review the literature on ultra-high field imaging of the amygdala with a field strength of 7 T or larger.

3. High-field imaging of the amygdala in non-clinical samples

3.1 Studies on functional activation of the amygdala

Ultra-high field imaging of the amygdala has been predominantly used in clinical studies. In non-clinical investigations, research has been done on functional and structural connectivity and functions of the amygdala. One of the earliest functional ultra-high field amygdala studies was published by Sladky et al. (2013), who studied activation of the amygdala and the bed nucleus of the stria terminalis (BNST) in response to emotional faces at 7 T. They demonstrated the superiority of ultra-high-field imaging in terms of better temporal and spatial resolution, a 100% signal increase, and better contrast by replicating and comparing bilateral amygdala activation during an emotion and an object recognition task between 7 T and 3 T methods. In a second experiment, they aimed to investigate activation

in the amygdala and BNST during the processing of emotional faces. They found increased activation in the central and basolateral amygdala and the BNST in response to visual emotion processing. Huggins et al. (2021) conducted a 7 T fMRI investigation on the neural substrates of fear generalization by presenting Gabor patches as visual stimuli in different angles varying between the angle of the secure CS- and the fearful CS+ which was followed by electric stimulation. They found a marginal negative fear generalization gradient (i.e., less activation due to high CS+ similarity) for the basal, but not the centromedial or lateral amygdala. Because of the small size of the BNST, Pedersen, Muftuler, & Larson (2017) used 7 T fMRI to visualize the effects of novelty, valence, and trait anxiety in the BNST, amygdala, and hippocampus. The hippocampus' response to the novelty of faces was independent of emotional valence. The BNST selectively responded to the novelty of only neutral faces whereas the amygdala only responded to the negativity of the faces. Interestingly, all these responses were blunted by high trait anxiety. Although not statistically significant, the authors found an interesting inter-hemispheric contrast: The right amygdala was more strongly activated when novel faces were fearful relative to neutral, while repeated faces elicited higher activation when they were neutral vs. fearful. The left amygdala exhibited an opposite pattern. Furthermore, reduced sensitivity to negativity due to high anxiety was limited only to the left amygdala. In a later study, the group around Pedersen demonstrated that the BNST, but not the centromedial amygdala, plays a crucial role in anxious anticipation of aversive stimuli (Pedersen et al., 2019).

Kreuder et al. (2020) studied the association between anxiety and fearful face processing from a neurochemical perspective. In their ultra-high field fMRI study, they found oxytocin and lorazepam to blunt the response of the centromedial amygdala to fearful vs. neutral faces. Both neuromodulators changed the intra-amygdalar connectivity of the

centromedial, basolateral and superficial (cortical) amygdala, whereas only oxytocin affected the connectivity between the centromedial amygdala and cortical structures. They concluded that anxiolytic medication may work by reducing amygdala activity and changing its connectivity.

Kragel et al. (2021) provided evidence for a functional colliculus-pulvinar-amygdala pathway encoding the intensity of normative emotional responses to negative emotional stimuli on the 7 T level. They suggested that this pathway portrays a functional "low road" processing of visual and auditory information. Aiming to validate these ultra-high field functional imaging results into context, Geissberger et al. (2020) investigated the systematic replicability of the bilateral amygdala activation in response to emotional faces. In each test run under varying experimental conditions, they were able to replicate the findings, and concluded that 7 T fMRI enables the mapping and parcellation of the amygdala in various ways in clinical and non-clinical settings.

In contrast to the validation of emotion processing studies by Geissberger et al. (2020), Murphy and colleagues (2020) conducted a methodological study on the limitations of ultra-high-field imaging. They investigated the validity of the results of activation patterns in the amygdala during a face-matching task using fMRI at 7 T, which were obtained by different spatial preprocessing steps. The combination of smoothing and motion correction yielded significantly different results. Specifically, differences in motion correction especially led to changes in the laterality of the activation in the amygdala and other subcortical and limbic structures. Thus, the authors uncovered a critical factor in the reproducibility of fMRI results on submillimeter resolution and put mixed results in ultra-high field studies in a new light.

3.2 Connectivity studies

In an extensive connectivity study by Klein-Flügge et al. (2022), all amygdala nuclei showed strong functional connectivity with the ventral caudal, medial frontal, and caudal orbitofrontal cortex. However, the basal and cortical amygdala had the strongest functional connectivity with those areas and negative correlations with lateral prefrontal regions, whereas the central nucleus was most strongly connected to subcortical and brainstem regions, underlining its role in autonomous activation in response to fearful stimuli. The connectivity between the lateral amygdala and the medial prefrontal cortex was identified as the strongest predictor for life satisfaction. Low functional connectivity between the basal amygdala and medial prefrontal regions and high connectivity between the central nucleus and subcortical areas were correlated to sleep problems. Furthermore, anger/rejection experience was associated with a lower negative correlation between the cortical amygdala and subcortical regions as well as between the lateral nucleus and cortical areas. Finally, negative emotion scores were predicted by functional connectivity between the nucleus accumbens and the basal and basomedial amygdala, and between the locus coeruleus and the lateral amygdala. In general, networks including the basal, cortical, and central amygdala were positively correlated with negative emotions.

Busler et al. (2019) examined functional connectivity patterns of the posterior cingulate cortex (PCC) and found, among other areas, the bilateral amygdalae to be co-activated and the left amygdala to be co-deactivated with the PCC. The authors assume a functional network for emotion processing in which the left amygdala is involved in processing fearful stimuli. Gorka et al. (2018) studied the intrinsic functional connectivity of the main output region of the amygdala, i.e., the central nucleus, and the bed nucleus of the stria terminalis. They found both regions to connect to areas of the middle prefrontal cortex,

the hippocampus, the thalamus, and the mesencephalic periaqueductal grey (PAG). The CeA (central nucleus of the amygdala) was more extensively coupled with the insula and sensory regions (i.e., thalamus and PAG) than the BNST, whereas the BNST was more closely connected to motivational and cognitive areas like the dorsal paracingulate cortex, the posterior cingulate cortex, and the striatum. Interestingly, these amygdalar structures showed asymmetric connectivity patterns: Overall, the left CeA was more extensively connected than the left BNST, while the right BNST was more connected than the right CeA. Further, the left CeA was more strongly connected than the right CeA. Torrisi et al. (2017) found functional connections between the habenula and the BNST, nucleus basalis, dorsal Raphé's nucleus, the ventral tegmental area, the PAG, the caudate nucleus, the thalamus, and cortical areas. Weis et al. (2019) examined the role of the extended amygdala's connectivity pattern in anxiety. They found the CeA and BLA to be strongly connected with parahippocampal, temporal, fusiform, and occipital areas, whereas the BNST appeared more strongly connected to the anterior caudate and cingulate cortex. Altogether, they could not give definite evidence of the relationship between the amygdala, trait anxiety, and tolerance of uncertainty.

Investigating the functions of the thalamus' paraventricular nucleus, Kark et al. (2021) found involvement of the amygdala in a network involved in episodic memory consolidation that they associated with the default mode network. In a functional 7 T parcellation study, Zhang et al. (2018) identified the centromedial, laterobasal, and superficial complexes as functionally homogenous subnuclei of the amygdala. They found correlations with various brain regions including cortical areas, basal ganglia, medial temporal lobes, limbic structures, and the cerebellum. The authors emphasized the role of the centromedial nucleus as the main output region for autonomous and motor functions. Further, they suggested the laterobasal

amygdala to be crucial for high-level visual processing and significance detection, associative learning, and the superficial nucleus for social interaction.

Interestingly, some subnuclei of the amygdala show hemispheric asymmetries in connectivity. Functional connectivity asymmetries were found mainly in the centromedial amygdala. In a structural 7 T study, Derix et al. (2014) found inter-hemispheric and interindividual variability of the amygdala-hippocampal border. This association was not further explained. However, it underlines the feasibility of ultra-high-field imaging in investigating microstructural differences in substructures of the amygdala and adjacent areas.

4. High-field imaging of the amygdala in psychiatric disorders

4.1 Major depressive disorder

Most clinical ultra-high field MRI studies of the amygdala investigated MDD. Several studies found decreased volumes of subnuclei of the left and right amygdala. In a recent review article, Cattarinussi and colleagues (2021) summarized 13 ultra-high field MRI studies on MDD. They describe inconsistent evidence for amygdala abnormalities in MDD: while most studies had found structural connectivity alterations, the literature on volumetric differences was still ambiguous. For example, using 7 T structural MRI, Brown et al. (2019) found the volumes of the bilateral centrocorticoid complexes and corticoamygdaloid transition area, the right lateral nucleus, and basolateral complex, and the left cortical and accessory basal nuclei to be negatively correlated with depressive symptom severity. The authors suggested a link between depressive symptoms and volume reduction in amygdala substructures of both hemispheres. This is in line with research from lower field strength imaging studies. On the 3 T level, decreased volumes of the right lateral and anterior amygdala as well as the

whole right amygdala were found in MDD patients (Kim et al., 2021). Using 4.7 T imaging, Aghamohammadi-Sereshki et al. (2021) found the right basal and accessory basal amygdala, the cortical amygdala subnuclei, and hippocampal areas to be smaller only in patients with MDD who had also experienced childhood trauma. In contrast, a 7 T study by Roddy et al. (2021) revealed increased rightward amygdala asymmetry in MDD that was driven by the right medial nucleus. Furthermore, the volume of the left cortico-amygdalar transition area was negatively correlated with the cortisol awakening response which, however, did not differ between patients and healthy controls. Lastly, in a treatment study by Kraus et al. (2019), MDD patients showed an enlarged right amygdala-hippocampal transition area and hippocampal fissure. Pharmacological therapy did not change these volumetric alterations. Brown et al. (2020) found increased structural connectivity of right lateral, basal, central, and centrocortical amygdala nuclei in MDD patients compared to healthy controls. These increases in connection density were driven by parts of the right stria terminalis and the right uncinate fasciculus. The left medial amygdala showed decreased connectivity. Since the central nucleus' projections to the hypothalamus are usually associated with stress responses (Kalin, Shelton, & Davidson, 2004), the authors assume a link to the dysregulated reactivity to stress found in depressive patients. Consistent with these findings, Jacob et al. (2022) found the degree of functional connectivity of the right central amygdala to correlate with depressive symptom severity. Altogether, these results inconsistently hint toward a relationship between bilaterally altered amygdala volumes, increased right-sided connectivity, and depression.

4.2 Bipolar disorder

In bipolar disorder, the amygdala, along with other limbic structures, is affected in terms of volume and structure (see Athey et al., 2021). To our best knowledge, Athey et al. (2012) were the only group to date to investigate structural changes in the hippocampi and amygdalae following lithium therapy at the 7 T level. They did not find volumetric alterations in the amygdala or hippocampi when comparing bipolar patients and healthy controls.

4.3 Psychotic disorders

Several studies have investigated amygdala involvement in psychotic disorders using ultra-high field imaging. Mahon et al. (2015) used 7 T parcellation of the amygdala to identify morphologic features of subregions which distinguish psychotic bipolar disorder from schizophrenia. Unlike Athey et al. (2021), they found significant atrophy of the left basolateral, basomedial, and centromedial amygdala in schizophrenia as compared to psychotic bipolar disorder. The right amygdala was atrophied in schizophrenia in comparison to psychotic bipolar disorder. Results for the right amygdala indicate a trend towards atrophy in schizophrenia and increased volume in bipolar disorder as compared to healthy controls.

4.4 Autism

Ultra-high field imaging has also proven useful to detect microstructural alterations in pathology. Fischi-Gomez et al. (2021) aimed to identify histopathological changes in autism spectrum disorder. They were able to visualize an increased grey matter density and abnormal laminar cytostructure in the bilateral amygdala and the right lateral orbitofrontal cortex in-vivo.

4.5 Sexual dysfunctions

Finally, in a 7 T graph analytical connectivity study, Chen et al. (2020) found the left amygdala's local efficacy to be negatively associated with premature ejaculation, state anxiety, and penile shaft sensitivity.

5. High-field imaging of the amygdala in neurological disorders

Other ultra-high field studies investigated amygdala involvement in various neurological disorders. For instance, Alper et al. (2021) aimed to assess structural alterations in trigeminus neuralgia using 7 T MRI. They targeted subcortical structures associated with stress and pain (i.e., amygdala, hippocampus, and thalamus) and found volume reduction of the basal and the paralaminar nucleus ipsilateral to the pain symptoms, alongside structural alterations in thalamic substructures. Oh et al. (2021) studied grey matter changes in patients with Parkinson's disease on a 7 T level. Besides prefrontal, hippocampal, and fusiform gyrus atrophy, there were significant volume reductions in the right, but not the left amygdala in patients with Parkinson's disease. Another 7 T study with drug-resistant epilepsy patients revealed an enlarged amygdala to be part of the epileptogenic zone in different subcortical and cortical networks (Makhalova et al., 2022). Contrary to the above-described findings, bilateral amygdala hypertrophy was positively correlated with depressive symptoms. These findings may be limited to epilepsy with depressive symptoms as comorbidity. Altogether, these results suggest an inconsistent involvement in neurological and psychopathological etiology models. Since these were the only ultra-high field studies on the amygdala that we were able to find, the evidence on neurological disorders and psychopathology (aside from MDD) is still sparse.

6. Discussion

The amygdala is a highly complex structure with a small overall volume. Ultra-high field imaging of the amygdala is, thus, indispensable to reliably investigate questions concerning clinic, connectivity, and function, since effects have been found on the subnuclear level. Therefore, the present work aimed to review recent studies on high-field imaging in the amygdala and synthesize their insights into the amygdala's connectivity, activity, and clinical relevance.

Using high-field imaging, evidence that was previously gathered on the whole amygdala can now be narrowed down to individual subnuclei or complexes and adjusted for confounding effects from other subnuclei. The current state of ultra-high-field imaging research is largely in line with lower-field findings and complements it with evidence on individual subnuclei. The findings presented above can be categorized as functional, connectivity, and clinical evidence. For a summary of nucleus-specific findings, see Table 2.

Insert table 2 here

Regarding distinct functions of the amygdala's subnuclei, several key insights were gained using ultra-high field imaging. Mostly these insights were gathered in the field of fear and emotion processing. It was found that the bilateral amygdala, especially the central and basolateral nuclei, and the BNST are involved in visual emotion processing. Moreover,

hemispheric asymmetries in the processing of valence and novelty were found. Further, the amygdala was identified as part of a “low road” pathway for processing the emotional intensity of negative visual stimuli. Finally, the basal amygdala and BNST were, although inconsistently, shown to play a crucial role in fear processing. Interestingly, however, no ultra-high field study replicated the involvement of the lateral nucleus as an input interface for potentially aversive stimuli in fear learning.

Connectivity analyses suggest that the amygdala is part of different functional networks. While it was bilaterally involved in networks associated with emotion processing and memory consolidation, the left amygdala was involved in processing fearful stimuli. In studies on the subnuclear level, the central amygdala functionally correlated with the insula and sensory areas, while the BNST appeared active in cognitive and motivational processes. Further, findings on functional networks including the amygdala support the centromedial amygdala’s main output function and attribute the role in social interaction to the superficial complex. Networks for the above-mentioned significance detection and associative learning processes included the laterobasal complex. In these investigations, only the central amygdala showed hemispheric asymmetries of functional connectivity, with stronger ipsilateral connectivity to the BNST and overall stronger connectivity of the left central amygdala.

Regarding clinical aspects, a major focus of high-field amygdala neuroimaging research has been MDD. Evidence for volumetric differences between patients and controls, however, is inconsistent. While volume reduction has been found in subnuclei of both hemispheres, some studies found a rightward volume asymmetry in MDD, supporting findings from lower field strength studies. Only a few studies investigated psychotic disorders, ASD, bipolar affective disorder, Parkinson’s disease, trigeminal neuralgia, and epilepsy. In all

diseases, alterations in the whole amygdala or subnuclear volumes were found. While there is evidence for the right amygdala to be atrophied in schizophrenia and enlarged in psychotic bipolar disorder (Mahon et al., 2015), others found no atrophy of the amygdalae in bipolar affective disorder (Athey et al., 2021). In ASD, increases in grey matter density and abnormal laminar cytoarchitecture could be found in both amygdalae. Reduced volumes were evident in Trigeminus neuralgia in the medial amygdala ipsilateral to the symptomatic side, and the right amygdala in Parkinson's disease. In epilepsy, a hypertrophic amygdala was shown to be part of the epileptogenic zone and was correlated with depressive comorbidity.

Interestingly, the study by Murphy et al. (2020) was the only one to explicitly address amygdalar functional and structural asymmetries with high-resolution MRI, although hemispheric differences have been found as "byproducts" in many analyses. A comprehensive review article by Ocklenburg et al. (2022) underlines the amygdala's asymmetric properties in terms of structure, function, connectivity, and clinical relationships. In general, the amygdala shows a robust volumetric rightward asymmetry which is mainly driven by a larger rightward asymmetry of the lateral nucleus, while other subnuclei show different patterns of lateralization. Further, there is evidence of leftward dominance for positively perceived stimuli (Young and Williams, 2013) and right-hemispheric dominance in processing negative emotional valence (Palomero-Gallagher and Amunts, 2021). Of note, this is in contrast to the above-described 7 T-findings in suggesting that the right rather than the left amygdala is crucial in recognizing fearful stimuli. Additional confounding effects in emotion processing studies may arise from the supposed leftward dominance for emotional language and a rightward dominance for visual emotional stimuli in the amygdala (Markowitsch, 1998). Moreover, temporal dynamics of the experiments are suspected to influence the amygdala's responses: the right amygdala may be more active when stimuli are

presented for sustained, long durations and cognitive processing, whereas the left amygdala may be dominant for short-term presentation and automated, subconscious processing. Ocklenburg et al. (2022) summarized this in three factors that are causal to the heterogeneous findings on amygdala asymmetry. They define a multimodal "TEP approach" with the factors being the temporal dynamics of experimental paradigm (T), the emotional valence of stimulus material (E), and perceptual stimulus properties (P). Thus, it appears necessary to manipulate these factors in functional and structural ultra-high field investigations and to link the structural asymmetries in terms of volume and structural connectivity to the functional asymmetries to obtain an overall, integrative picture.

7. Implications for future research

High-field imaging of the amygdala is still an emerging field in clinical and basic neuroscience, and the results of the studies presented in the previous sections hold several implications for future research projects. Due to differences in hemispheric asymmetries between subnuclei, it is imperative to study the amygdala's functional and structural asymmetries on a deeper level instead of viewing it as a whole structure. It seems reasonable that this approach may solve the inconsistencies and replicability issues of findings on amygdala asymmetries.

Like psychology, neuroscience faces a severe replication and reproducibility crisis (Miłkowski et al., 2018). Apart from theory-driven suggestions like differential subnuclear influences on whole amygdala function, further questions related to replicability remain significantly under-researched in high-field amygdala imaging. Specifically, methodological peculiarities of high-field imaging must be considered. Different preprocessing methods have been shown to drastically influence functional imaging results and should be taken into

account when comparing and interpreting findings. Also, researchers should make sure to report the precise MRI methods to facilitate replicability and comparability. These considerations may counteract a portion of the inconsistent results and must, thus, be established as soon as possible in the still young field of ultra-high-field imaging.

To answer the open questions in the current literature, it appears crucial to study the structural and functional properties and connectivity of the amygdala under consideration of the TEP approach. To vary the modality and valence of stimulus material, future investigations could compare responses to positive, negative, or neutral faces or images, the latter taken from the International Affective Picture System, for instance (Lang et al., 1997). Additionally, auditory and written stimuli of varying valence should be included to obtain separate results for different modalities of language processing. For the temporal dynamics, the level of awareness of processing could be manipulated using backward masking (Gläscher and Adolphs, 2003; Morris et al., 1998). To minimize confounding effects due to hemispheric asymmetries in habituation rates of the two amygdalae, the stimuli should be presented in a randomized order. Once the three TEP variables are functionally associated with specific subnuclei, these could serve as regions of interest for analyses of volumetric properties and connectivity analyses of the amygdala. This way, researchers would be able to obtain a comprehensive image of how structural amygdala asymmetries give rise to functional asymmetries.

Given the high clinical relevance of the amygdala for affective and anxiety disorders, it will be crucial to understand how key factors involved in the pathogenesis of these disorders affect amygdala structure and function in high resolution. Only few studies have investigated the subnuclear microstructure of the amygdala in fear learning in humans. Schlüter et al. (2022) showed that neurite density in the lateral amygdala was correlated with neuroticism

in humans. However, the parcellation did not fully succeed due to low spatial resolution at 3 T. Moreover, despite the asymmetric processing of emotional stimuli, the authors did not investigate interhemispheric differences. Thus, future studies should examine the microstructure and connectivity of all subnuclei on an ultra-high field level to apply the theoretical foundations of amygdala functioning to clinical research questions. Specifically, the amygdala's function as a relay for incoming emotional stimuli and further processing could be experimentally simulated with a fear conditioning paradigm or presentation of fearful faces while measuring the functional and structural connectivity and the BOLD response of individual subnuclei and their microstructure using Neurite Orientation Dispersion and Density (NODDI) analyses. Following this idea and previous 7 T findings, the interindividual neurite density in the lateral nucleus should correlate with the BOLD response of the lateral, basal, and central amygdala, as well as the BNST. For negative emotional stimuli, according to Palomero-Gallagher and Amunts (2021), these relationships should be stronger in the right than in the left hemisphere. However, a 7 T study by Busler et al. (2019) suggested a left-hemispheric dominance in processing fearful stimuli. This ambiguity remains to be resolved, as well.

In summary, future studies should apply ultra-high field MRI on theoretical considerations about hemispheric asymmetries in function, microstructure, and connectivity of amygdala subnuclei and systematically manipulate temporal characteristics, emotional valence, or perceptual properties of the stimuli to obtain a comprehensive overview of the determinants of subnuclear amygdala functioning, especially regarding hemispherical differences in functional activity. Combining these insights with structural and connectional information could yield a holistic picture of the mechanisms underlying amygdala functions and psychopathological developments for example in anxiety disorders.

8. Conclusion

Taken together, the studies reviewed in the present article clearly show that ultra-high field imaging is an emerging field that offers new perspectives to study the underlying mechanisms of amygdala functions. The presented studies underline the important role and suggest interesting hemispherical asymmetries of the central, basal, basolateral, and extended amygdala in fear and emotion processing, and describe widespread connectivity patterns involving networks for learning and memory, stimulus processing, as well as cognitive and social processes. Most clinical ultra-high field research in MDD patients suggests either an overall rightward atrophy of the amygdala or differential volume increases and decreases in different bilateral subnuclei, with the medial nucleus, conversely, driving a rightward enlargement of the amygdala. Structural alterations in other pathologies like bipolar affective disorder or psychotic disorders were found as well. However, the evidence on fear and emotion processing and connectivity on ultra-high field level is still sparse and ambiguous, partly due to methodological and conceptual differences, leaving room for further comprehensive investigations.

Declaration of Competing Interest

The authors declare no competing interests.

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Tables

Table 1. Overview of previous findings on the functions of the amygdala subnuclei

Nucleus	Function
Anterior amygdalar area	Configural conjunction of fearful eye and mouth movements (left; (Morris et al., 2002)
Accessory basal nucleus	Top-down control of anxiety and fear, fear extinction in mice (Adhikari et al., 2015)
Amygdalocortical transition area	Delivers hippocampal input of emotional context of memories to the central amygdala (Fudge and Tucker, 2009)
Amygdalohippocampal area	Emotional learning and memory (McDonald and Mott, 2017)
Amygdalohippocampal transition area	Sociosexual behavior and cognitive functions (Sedwick and Autry, 2022)
Amygdalostriatal transition area	Fear learning under stress (Goto et al., 2022)
Basal nucleus	The bridge between the lateral (input) and central amygdala (output), is involved in fear expression and extinction (Amano et al., 2011), contextual control after fear extinction (Orsini et al., 2011), learning active fear coping responses (Phelps and LeDoux, 2005)
Central nucleus	Main output region, behavioral and autonomous fear responses (Phelps and LeDoux, 2005), feedback to the lateral amygdala (Yu et al., 2017)
Cortical nucleus	Aversive and appetitive odor-driven behavior (Root et al., 2014), selective processing of social stimuli (Goossens et al., 2009)
Endopiriform nucleus	/[a]
Intercalated nucleus	Regulates switch between low- and high-fear states (Hagihara et al., 2021), relay function in the expression of fear extinction (Likhtik et al., 2008)
Intramedullary gray of the amygdala	/[a]
Lateral nucleus	Sensory input, key site of plasticity (Phelps and LeDoux, 2005)
Medial nucleus	Olfactory processing, innate emotional behavior for reproduction and defense (Keshavarzi et al., 2014), processing social signals, and regulating social behavior (Raam and Hong, 2021)
Paralaminar nucleus	Close to projections involved in contextual fear learning (deCampo and Fudge, 2012)

Annotations. [a] subnuclei have not been an object for research yet, nor have been explicitly functionally described in previous publications.

Table 2. Overview of ultra-high field research findings on amygdalar subnuclei.

Nucleus	Findings
Anterior amygdalar area	Decreased volume in MDD (right; Kim et al., 2021)
Accessory basal nucleus	Decreased volume in MDD (left; Brown et al., 2019)
	Connectivity with the nucleus accumbens predicted negative emotions (Klein-Flügge et al., 2022)
	More strongly atrophied in schizophrenia than in psychotic bipolar disorder (Mahon et al., 2015)
Amygdalocortical transition area	Decreased volume in MDD (bilateral; Brown et al., 2019)
	Negatively correlated with the cortisol awakening response (left; Roddy et al., 2021)
Amygdalohippocampal area	*No ultra-high field findings*
Amygdalohippocampal transition area	Increased volume in MDD (right; Cattarinussi et al., 2021)
	Inter- and intraindividual variety (Derix et al., 2014)
	Increased volume in MDD (right; Kraus et al., 2021)
Amygdalostriatal transition area	*No ultra-high field findings*
Basal nucleus	Decreased volume in trigeminal neuralgia (Alper, 2021)
	Decreased volume in MDD after childhood maltreatment (right; Aghamohammadi-Sereshki et al., 2021)
	Increased connectivity in MDD (right; Brown, 2020)
	Decreased volume in MDD (right; Brown, 2019)
	Negative fear generalization gradient (Huggins et al., 2021)
	Low connectivity with medial PFC predicted sleep problems; connectivity with nucleus accumbens predicted negative emotions (Klein-Flügge et al., 2022)
	Basolateral & basomedial atrophied more in schizophrenia than in psychotic bipolar disorder (Mahon et al., 2015)
	Basolateral: visual emotion processing (Sladky et al., 2013)
	Laterobasal: significance detection and associative learning (Zhang, 2018)

Central nucleus	Nociception, left anti-nociceptive (Allen et al., 2021)
	Increased structural connectivity in MDD (right; Brown, 2020)
	Bilateral centrocorticoid and left central volumes negatively correlated with depressive symptom severity (Brown et al., 2019)
	Coordination of responses to sensory stimulation (Gorka et al., 2018)
	Functional connectivity correlates with depressive symptom severity (right; Jacob et al., 2022)
	Stress response (Kalin et al., 2004)
	Involved in networks correlating with negative emotions; strong connectivity with subcortical and brainstem regions; high connectivity with subcortical areas predicted sleep problems (Klein-Flügge et al., 2022)
	OXT and LZP inhibit response to fearful faces. OXT increases connectivity with BLA, dmPFC, and precuneus. LZP increases the connectivity of the left centromedial with the right SFA (Kreuder et al., 2020).
	Stronger atrophy in schizophrenia than in psychotic bipolar disorder (Mahon et al., 2015)
	Visual emotion processing (Sladky et al., 2013)
	Centromedial: Main output region for autonomous and motor functions (Zhang et al., 2018)
Cortical nucleus	Decreased volumes in MDD (left; Brown et al., 2019)
	Increased structural connectivity in MDD (right; Brown et al., 2020)
	Low negative connectivity with subcortical regions predicted feelings of anger/rejection; involved in networks for negative emotions (Klein-Flügge et al., 2022)
	LZP enhances functional connectivity between the left centromedial and right superficial complex in response to fearful faces (Kreuder et al., 2020)
	Superficial complex: olfactory information, social interaction (Zhang et al., 2018)
	Centrocorticoid complex: see "Central amygdala"
Endopiriform nucleus	*No ultra-high field findings*
Intercalated nucleus	*No ultra-high field findings*
Intramedullary gray of the amygdala	*No ultra-high field findings*

Lateral nucleus	Decreased volume in MDD (right; Brown, 2019)
	Increased connectivity in MDD (right; Brown, 2020)
	Connectivity with the medial prefrontal cortex predicted life satisfaction; low connectivity with cortical areas during anger/rejection; connectivity with locus coeruleus predicted negative emotions (Klein-Flügge et al., 2022)
	Basolateral complex: see "Basal nucleus"
Medial nucleus	Decreased connection density in MDD (left; Brown, 2020) Enlarged in MDD (right; Roddy et al., 2021)
	Centromedial complex: see "Central nucleus"
Paralaminar nucleus	Decreased volume in trigeminal neuralgia (Alper, 2021)

Annotations. BLA = basolateral amygdala; dmPFC = dorsomedial prefrontal cortex; LZP = Lorazepam; OXT = Oxytocin; SFA = superficial amygdala (composed of the cortical amygdala and olfactory nucleus).

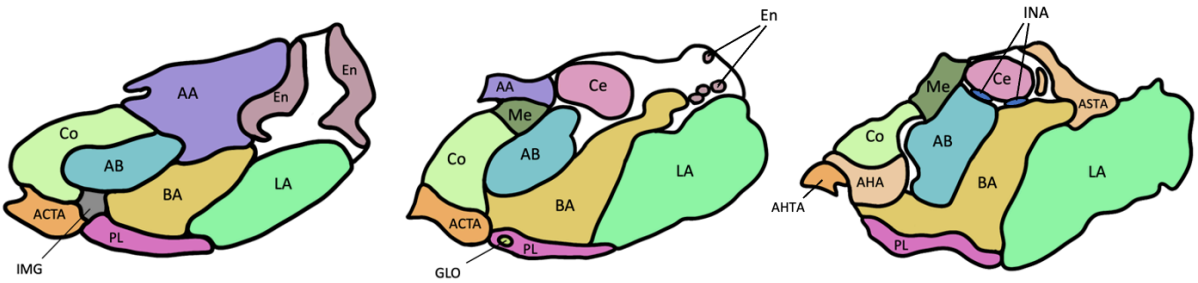

Figure 2. Schematic illustration of the subnuclei of the left human amygdala. From left to right, the amygdala is shown in an anterior, medial, and posterior frontal section, viewed from an anterior perspective. White areas show undescribed amygdala matter. AA = anterior amygdala area; AB = accessory basal (or basomedial) nucleus; ACTA = amygdalocortical transition area; AHA = amygdalohippocampal area; AHTA = amygdalohippocampal transition area; ASTA = amygdalostriatal transition area; BA = basal nucleus; Ce = central nucleus; Co = cortical nucleus; En = endopiriform nucleus; INA = intercalated nuclei; IMG = intramedullary gray of the amygdala; LA = lateral nucleus; Me = medial nucleus; PL = paralaminar nucleus. Based on the cellular-resolution atlas by Ding et al. (2016).