

Functional organization of the human amygdala in appetitive learning

Emilia Kolada¹, Krzysztof Bielski¹, Marcel Falkiewicz², and Iwona Szatkowska^{1*}

¹Laboratory of Psychophysiology, Nencki Institute of Experimental Biology, Warsaw, Poland, ²Max Planck Research Group Neuroanatomy & Connectivity, Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany,

*Email: i.szatkowska@nencki.gov.pl

The amygdala is a small subcortical structure located bilaterally in medial temporal lobes. It is a key region for emotional processes and some forms of associative learning. In particular, the role of the amygdala in processing of negative emotions and aversive learning has been shown in numerous studies. However, involvement of this structure in processing of positive affect and appetitive learning is not fully understood. Previous experiments in animals are not consistent. While some authors implicate only the centromedial part of the amygdala in appetitive learning, the others suggest contribution of both centromedial and basolateral subregions. Although from the evolutionary perspective appetitive learning is equally important as aversive learning, research on the role of the human amygdala and its subregions in appetitive learning is undertaken relatively rarely and the results are not conclusive. Therefore, the aim of this review is twofold: to summarize the current knowledge in this field and to indicate and discuss the factors, which might affect the observed level of the amygdala activity during appetitive learning in humans.

Key words: amygdala subdivisions, associative learning, reward learning, reinforcement, functional magnetic resonance imaging (fMRI)

INTRODUCTION

Associative learning is a process in which the association between two stimuli or a stimulus and a reaction is acquired. Importantly, this process can be further differentiated into appetitive and aversive learning if the primarily neutral stimulus or action is paired with the pleasant or unpleasant event, respectively. Both reward-based and punishment-based learning are typically studied by means of Pavlovian and operant conditioning paradigms. However, while aversive conditioning (e.g. fear conditioning) has been intensively investigated in both animals and humans through the decades, surprisingly little is known about the neural underpinnings of appetitive processes. Recent methodological developments, as well as emergence of theories emphasizing the role of incentive learning in formation of different types of addictions (Everitt et al. 2001, Carey et al. 2014), eating disorders (Södersten et al. 2006), depression (Whitton et al. 2015) and other disorders has led to the growth of interest in appetitive conditioning and its neural correlates.

So far, the investigations of appetitive conditioning in non-human species reported increased firing of neurons in the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC), the striatum, the amygdala and

the midbrain structures (i.e. the ventral tegmental area and the substantia nigra) (for a review, see Cardinal et al. 2002). These observations are fairly consistent with the less numerous studies in humans. However, although the role of the OFC, the striatum and the mesolimbic dopaminergic system in appetitive conditioning is convergent with established knowledge about neural circuitry supporting appetitive learning process, role of the amygdala remains not fully understood. Therefore, the aim of this article is to review the current literature concerning involvement of the amygdala in appetitive learning with special interest in the studies in humans. Firstly, the structural diversity of the amygdala will be shortly described; secondly, we will summarize the outcomes of the animal studies on the role of distinct amygdalar nuclei in appetitive conditioning and review few attempts to specify the functional diversity of the amygdala in humans. Finally, we will summarize the factors which are most likely to contribute to the variation in the observed activations of the amygdala in humans.

THE ANATOMY OF THE AMYGDALA

The amygdala is a small subcortical structure located bilaterally in the medial part of the temporal lobe. Despite

of its small size, the amygdala is an anatomically and functionally diverse structure consisting of approximately 13 nuclei (Freese and Amaral 2009). On the basis of anatomical evidence the classification of this brain structure into three distinct subdivisions was proposed. According to McDonald (1998) the amygdalar nuclei can be separated into three groups: superficial, centromedial (CMA) and basolateral (BLA).

The superficial group comprises the cortical nucleus, the nucleus of the lateral olfactory tract and the periamygdaloid cortex (McDonald 1998). It can be characterized by strong connections with the olfactory and accessory olfactory bulbs and cortex-like structure with pyramidal cells oriented perpendicularly to the brain surface (Swanson and Petrovich 1998), forming the most outer part of the amygdala. The basolateral part encompasses lateral (LaA), basal (BaA) and accessory basal nuclei (aBaA) (McDonald 1998). The neural cells of the BLA exhibit similarity to the pyramidal and non-pyramidal cortical cells (McDonald 1998) and are dominated by the glutamatergic neurotransmitter system (Swanson and Petrovich 1998). The BLA is strongly connected with the cortical areas. In particular, basal and accessory basal nuclei receive rich projections from the orbital and the medial cortex, the anterior cingulate cortex and the insula, while lateral nucleus receives neocortical inputs from the insula, the superior temporal gyrus and the visual and the associative visual areas (Stefanacci and Amaral 2002). Finally, the centromedial group includes the central (CeA) and the medial (MeA) nuclei. Swanson and Petrovich (1998) argue that the CeA is the phylogenetically oldest part of the amygdala and originates from the striatum. Contrary to the other two groups of nuclei, its extrinsic projections are principally formed with GABAergic cells, which are also the main substrate of the striatal connections. The CeA has abundant bidirectional connections with the brainstem and hypothalamus, but also receives information from the cortical regions (particularly from the insula and the OFC) and the thalamus (for reviews, see McDonald 1998, Swanson and Petrovich 1998, Knapska et al. 2007).

FUNCTIONAL DIVERSITY OF THE AMYGDALAR NUCLEI IN ANIMALS

The amygdala has been demonstrated to play the essential role in processing of emotions (for a review, see Zald 2003) and their expression (see a review in Davis and Whalen 2001), detection of salient stimuli (see discussion in Sander et al. 2003), value assessment in decision-making (for a review, see Pessoa 2010) and associative learning (e.g., Everitt et al. 2003, for a review, see Baxter and Murray 2002). In particular, considerable attention has been devoted to understand the function of the amygdala in

fear conditioning (e.g. Knapska et al. 2012, for a review, see Cybulska-Klosowicz 2016). Yet, it is now indisputable that this structure is involved not only in aversive conditioning but also reward learning.

Early evidence comes from the lesion studies in monkeys. For example, Gaffan and others (1988) trained the monkeys in learning the association between a visual stimulus and a food reward. The monkeys had to choose one of 2 stimuli presented on the screen, only one of which was paired with the reward. After a proper training the monkeys underwent a surgery and the inferotemporal cortex (the visual association area) was removed. As expected, this intervention did not impair the learning ability. Next, the authors carried out ablation of the contralateral amygdala. They observed that the disconnection of the amygdala from the contralateral inferotemporal cortex severely hinders learning the association between a visual stimulus and a reward. Experimental ablation was also used in primates to demonstrate the significance of the amygdala in such learning-related processes as reversal learning (Aggleton and Passingham 1981, Spiegler and Mishkin 1981, but see Izquierdo and Murray 2007), reinforcer devaluation (Málková et al. 1997, Izquierdo and Murray 2007), conditioned orienting (McDannald et al. 2004) or reward anticipatory autonomic response (Braesicke et al. 2005). Importantly, on the basis of these observations the role of the amygdala in appetitive learning has been hypothesized.

There is considerable evidence that the central nucleus of the amygdala plays a key role in reward learning. Seminal study by Parkinson and others (2000) indicated that only the CeA is indispensable for appetitive learning to occur as measured by the conditioned approach response directed towards the cue (conditioned stimulus, CS). Moreover, it was shown that the CeA is not necessary for expression of this behavior. Instead, it is essential for rodents to learn conditioned orienting responses (McDannald et al. 2004). Studies at the molecular level also demonstrated selective engagement of the CeA in appetitive learning (Knapska et al. 2006, 2013). For example, Knapska and colleagues (2013) showed that activity of matrix metalloproteinase-9 (MMP-9), an enzyme involved in learning and memory, is enhanced in the extracellular matrix of the CeA after appetitive, but not aversive training. What is more, blocking extracellular MMP-9 activity with its inhibitor TIMP-1 severely impairs appetitive learning in mice, but has no effect on the aversive learning. In addition, stimulation of the CeA mu opioid (DiFeliceantonio and Berridge 2012) and oxytocin (László et al. 2016) receptors enhance incentive salience of a cue paired with a food reward and preference towards a place associated with drug injection, respectively. Both stimulants are believed to act upon the mesolimbic dopaminergic system via its connections with the central nucleus of the amygdala. Finally, it is worth to

note that there are two psychological components of the reward: motivational ('wanting') and emotional ('liking'). It has been shown that CeA is specifically associated with 'wanting' of the reward (Mahler and Berridge 2012), although more recent study has suggested that disruption of neurons within the CeA with electrical impulses decreased both 'wanting' and 'liking' value of the reward (Ross et al. 2016). All these observations point to appetitive learning as being determined by activity of neuronal cells within the central nucleus of the amygdala.

On the contrary, Paton and others (2006) used single neuron recording to investigate the neural representation of positive and negative values of conditioned stimuli during learning. They found that the populations of neurons responding selectively to rewards (food) or punishment (air-puff) did not show consistent anatomical mapping. Baxter and Murray (2002) suggested that both, basolateral and centromedial groups of nuclei subserve the reward learning, but their functions are distinct and complementary to each other. According to their view, basolateral group of nuclei is predominantly implicated in acquiring associations between a neutral cue and a current incentive value of an unconditioned stimulus (US), as demonstrated by BLA lesion that impairs evaluation of reward value in monkeys (Málková et al. 1997), potentiated feeding behavior in response to conditioned stimulus (Holland et al. 2001) and US-specific Pavlovian-to-instrumental transfer (Corbit and Balleine 2005). On the other hand, proposed function of the CeA is development of Pavlovian approach response towards a CS as a result of learning. Close to this interpretation is the model of parallel-processing proposed by Moscarello and LeDoux (2013) which assumes that the BLA encodes associations between a CS and a specific feature of a US, whereas the CeA is essential for linking a CS with a generalized behavioral reaction.

THE AMYGDALA AND THE REWARD LEARNING IN HUMANS

In humans, the selective lesions of the amygdala, which is a common technique applied in animal studies, are extremely rare. One instance of selective damage of the amygdala in humans is caused by calcification of this structure in patients with Urbach-Wiethe disease (Appenzeller et al. 2006). The first investigation of associative learning in a patient with bilateral amygdala damage was performed by Bechara and others (1995), who measured skin conductance response to the cue paired with an aversive auditory stimulus in healthy subjects, a patient with bilateral amygdala lesion, a patient with damage of the hippocampus and a patient with damage of both, the amygdala and the hippocampus. They found that

only the subjects who suffered from amygdala loss, either alone or in conjunction with hippocampus destruction did not learn the aversive association. Siebert and colleagues (2003) examined comprehensively a group of 10 patients with Urbach-Wiethe disease. They assessed perception of facial emotions, episodic memory of positive and negative pictures and emotional learning as measured with figure – odor association test. The results of the association test revealed impaired learning of pairs of neutral (nonsense drawing) and emotional (appetitive odor) stimuli.

Despite of the fact that patients with Urbach-Wiethe disease may provide valuable information about the role of this structure as a whole, they cannot be applied to study the functions of the distinct amygdalar subdivisions. Such opportunity is provided by functional magnetic resonance imaging (fMRI) – a technique, which relies on blood-oxygen-level dependent (BOLD) signal and allows to examine *in vivo* activation of brain structures during various mental tasks. Indeed, the technique was proven to be suitable to investigate associative learning mechanisms in human subjects (O'Doherty et al. 2002, Gottfried et al. 2003, Valentin et al. 2007, Klucken et al. 2013). Yet, the vast majority of these studies treated the amygdala as a homogeneous structural unit. The issue of functional diversity of the human amygdala was probed in the research on emotional processing using facial expressions (Hurlemann et al. 2008) and auditory stimulation (Ball et al. 2007) demonstrating that functional dissociation of the amygdalar subregions with fMRI is possible. To our best knowledge, heretofore, the problem of functional organization of the human amygdala in reward learning-related procedures was undertaken by only four studies conducted by two laboratories. The experiments are described in detail below.

In the first study, Davis and colleagues (2010) used classical conditioning paradigm to investigate which amygdalar subregions are responsive to appetitive and aversive learning. They paired three neutral faces with neutral, positive or negative self-relevant sentences. In this way, the different individuals predicted neutral, positive or negative social outcomes. Behavioral results, measured with pre- and post-likeability ratings of each face, confirmed that the subjects learned the associations. The fMRI results indicated three distinct spatial patterns of activation in the amygdala. First, the medial ventral part corresponding to basal nucleus of the amygdala showed robust activation in the early phase of conditioning in response to all three faces predicting neutral, positive and negative outcomes. Second, the dorsal subregion of the amygdala and the substantia innominata were activated when the faces predicted either negative or positive social outcome. As in medial ventral part, neuronal response was stronger at the beginning of experiment. Last, increase of BOLD signal in the lateral part mapped to the lateral nucleus

of the amygdala was predominantly observed in negative condition. Moreover, only this part revealed relatively constant pattern of activation throughout the whole session. In this experiment, increase in BOLD signal correlated with reward prediction was unselectively present in the CeA and the BaA. Since human faces could be themselves considered salient stimuli and because the BaA was active in all three conditions, this could be interpreted as that the BaA plays an important role in processing of biologically significant events. On the contrary, the CeA could be engaged in learning the associations between neutral and emotional (but also arousing) stimuli. Unfortunately, the authors did not report whether any activation was specific to the appetitive condition alone, which restricts further inference about functional organization of the human amygdala in appetitive learning.

In another experiment, Prévost and others (2011) attempted to clear the role of groups of the amygdalar nuclei in reward learning using operant conditioning paradigm. Subjects were presented with a reward, aversive or a neutral cue (CS) which was then followed by appearance of a two-armed bandit slot machine. Participants had to select the action (i.e. left or right arm). Each cue was associated with one “correct” response, which led to monetary gain in reward condition with 80% probability and no monetary gain with 20% probability or no monetary gain with 80% probability in aversive condition and monetary loss with 20% probability. This proportion was reversed after four consecutive correct actions to maintain the level of uncertainty. In neutral condition participants neither won or lost any money regardless of the action they selected. To specify the regions of the amygdala the authors performed a manual parcellation of the structure into basolateral, centromedial and cortical subdivisions. Next, they analyzed the brain response at the time of action selection, unexpected outcome of the action (error prediction) and cue presentation. Interestingly, in the reward condition BOLD signal in the BLA correlated positively with the action value, whereas in the aversive condition the CMA revealed higher correlation with the action value. Error prediction correlated positively with the enhanced activity in the BLA regardless of the condition. Finally, cue-related activity was found only in the aversive condition in CMA. No significant activity in reward condition was found at the time of cue presentation. These results are difficult to interpret since they appear contradictory to the hypothesis of the key role of the CeA in reward learning. However, the monetary loss which was avoided by the subjects who preferentially chose the correct response should not be interpreted as an aversive condition. Avoiding a punishment should rather be perceived in terms of rewarding experience. Moreover, as the authors admitted, the financial reward might be processed in a different manner than the primary reinforcers, which are used in animal research.

Thus, in their next experiment, Prévost and colleagues (2013) used primary reinforcers in a Pavlovian paradigm. In appetitive session subjects learned associations between one cue and the pleasant liquid delivered 60% of the time and another cue and the neutral flavor stimulus delivered with the same reinforcement schedule. In aversive session, with the probability of 0.6 the first and the second cues were followed by the aversive or neutral liquids, respectively. The procedure also involved reversal learning, such that the cue associated with the affective outcome, after 16 trial predicted the neutral stimulus and the cue paired with the neutral outcome predicted the affective one. Interestingly, expectancy of the pleasant stimulus in appetitive session correlated with the activity in the BLA of the right amygdala, while the expectancy of the unpleasant stimulus correlated with the activity in the CMA of the left amygdala.

The fourth study, also by Prévost and others (2012) investigated the Pavlovian-to-instrumental transfer (PIT), a well-known learning phenomenon which combines classical and instrumental conditioning. In particular, they were interested in the mechanisms underpinning the two forms of PIT: outcome-specific and general. In line with evidence from animal research, specific PIT which is manifested with increase in response associated with a specific outcome was correlated with BOLD activity within the basolateral amygdala and ventrolateral putamen. Conversely, successful general PIT which is linked to increase in response to reward trials, regardless of the reward type, as compared to neutral trials, correlated to BOLD activity within the boundaries of the CMA. Since the conditioned stimuli used in this experiment were only appetitive (food rewards), this result seems to correspond well to the model proposed by Moscarello and LeDoux (2013).

The reviewed studies on the functional organization of the amygdala in humans are not sufficient to verify the hypotheses of selective involvement of the amygdalar nuclei in appetitive learning developed based on animal experimentation. The studies by Davis and colleagues (2010) and Prévost and others (2013) are disparate with the respect to applied procedure (Pavlovian vs. operant conditioning), type of reinforcement (social vs. monetary) and conditions (positive and negative vs. reward and punishment avoidance). Nevertheless, they prove that investigation of the amygdala at the level of individual groups of nuclei rather than at the level of the whole structure using fMRI in humans should be valuable direction for future studies. Another important consideration arising from this review throws light on the methodological and technical constraints which may undermine the obtained results and diminish reproducibility of such experiments. Some of these factors are category of reinforcement, stimulus sample

and data analysis strategies, and the approach to defining the subdivisions of the amygdala. Impact of each will be shortly discussed.

CHALLENGES OF MEASUREMENT OF THE HUMAN AMYGDALA

Reinforcement type

One classification of reinforcers differentiates between primary and secondary rewards. The former are represented by foods, drinks or erotic stimuli. They hold an intrinsic motivational value since their accessibility is crucial for the survival of individual organisms and species. The latter are more abstract (e.g., money). Their value is established on the basis of learned associations with primary rewards, thus they can help to maintain the internal stability of an organism only indirectly and not immediately.

Since the hypotheses of the functional organization of the amygdala have evolved from the studies in animals, testing these models in humans requires the use of as similar paradigms and stimuli as possible. Therefore, it seems rational to use the primary reinforcers in the first place. Nevertheless, previous research on appetitive conditioning in humans utilized both, primary and secondary rewards to reinforce the neutral cue. Activation of the amygdala was observed in the studies using odor (Gottfried et al. 2003), liquids (O'Doherty et al. 2002, Metereau and Dreher 2013, Prévost et al. 2013, Kerr et al. 2015, but see Valentin et al. 2007), erotic pictures (Klucken et al. 2013) and money (Prévost et al. 2011). However, while most of the studies using primary reinforcers found BOLD activity in the amygdala, the results of many experiments using financial gains are inconsistent. For example, while Prévost and colleagues (2011) demonstrated increased signal in the amygdalar subregions when selecting the action leading to monetary reward in their instrumental learning task, others (Kirsch et al. 2003, Cox et al. 2005, Puschmann et al. 2013) did not report any activity in this structure. Metereau and Dreher (2013) carried out an experiment based on Pavlovian conditioning procedure in which they compared the activity related to error prediction in four conditions: two aversive using primary reinforcers of different modalities (salty water, picture of injured person) and two appetitive, one primary (pleasant juice) and one secondary (monetary gain). Conjunction analysis of error prediction response in three conditions using primary rewards revealed that the common activation site is the amygdala. Furthermore, direct contrast of this response with the response to omission of the secondary reinforcer showed that the left amygdala in particular is sensitive to the former, but not the latter.

Stimuli and data analysis implications

It is assessed that the results of over 60% of fMRI studies might be profoundly overestimated being a consequence of false assumptions incorporated into the standard model of fMRI data analysis (Westfall et al. 2016). Although the problem of stimulus variation has been emphasized (Donnet et al. 2006, Bedny et al. 2007, Westfall et al. 2016), the traditional approach assumes that neural response to all stimuli belonging to the same category is equal. This belief, often referred to as the stimulus-as-fixed effect, in some circumstances may result in increase in number of false positive errors and consequently, incorrect inferences. To illustrate this, Westfall and colleagues (2016) used the dataset from the Human Connectome Project (HCP) to compare the results produced under the standard and random stimulus models. The HCP Emotional Processing Task (Barch et al. 2013), in which subjects are presented with either facial expressions (angry or fearful, 10 different face stimuli per condition) or geometric shapes, is a well-documented example of amygdala activation in response to biologically salient and unpleasant events. Amygdala's activity has been shown to vary substantially between specific faces within the same condition. This variability can be taken into account in a random stimulus model (RSM). The authors have shown that the test statistic for the contrast between emotional and neutral stimuli is inflated in the standard model by 89% as compared to the test statistic calculated in the RSM. As a consequence, data modelled with RSM did not reveal any differences in the amygdala activation in contrast between angry and fearful faces, while analysis using the standard model pointed to the slightly but significantly stronger response of the amygdala to anger. According to Westfall and others (2016), these false alarms generated under the standard model can be avoided if stimulus sample size is increased substantially. Nevertheless, this appeal might be strongly constrained or even impossible to apply due to the nature of an experimental stimulus (e.g. gustatory or olfactory stimulus, electric impulse). On the surface, use of one stimulus per condition resolves the problem since there is no stimulus variation which would be neglected. However, exposure to only one or even a small number of events brings another risk: a rapid habituation of amygdala response, which is a well described effect in the literature.

The amygdala is a saliency detector, therefore it responds rapidly to relevant and emotionally significant stimuli. But because constant activation is energetically expensive, the neurons within the amygdala habituate very quickly, if a particular event is not followed by any harmful or pleasant consequences. This decrement in activity was observed in response to novel stimuli (Blackford et al. 2010), repeated emotional events (Fischer et al. 2003) and associative learning regardless of the

reinforcer valence (Gottfried et al. 2002, Baeuchl et al. 2015). This phenomenon was observed in animals (Quirk et al. 1997) and humans (Wedig et al. 2005, Davis et al. 2010), although not all the subregions habituate with the same rate and to the same extent (Morris et al. 2001, Repa et al. 2001). Gradual decrease in BOLD signal during learning experiment across subsequent trials might be troublesome. The robust activation of the amygdala usually present at the beginning of experimental session could potentially pass unnoticed, since lower averaged response may not survive statistical thresholding. The researchers came up with several solutions to this problem. For example, in the study described by Prévost and others (2011) the authors used partial reinforcement schedule, which increases the uncertainty and prolongs the learning process. Also, after four consecutive correct responses the proportions of the reinforcement were reversed increasing the ambiguity and preventing from quick habituation. Another widely applied solution is dividing the training into time bins. Davis and colleagues (2010) calculated BOLD signal separately for the early (first half) and late (second half) phases of the conditioning. The revealed high activity to the significant cues in basomedial and centromedial subdivisions in the early, but not in the late phase. Another common method of considering time-related changes in the amplitude of BOLD signal is to model them on trial-by-trial basis, as a covariate. However, application of this approach is strongly limited in case of the amygdala due to nonlinear changes of signal in this structure and low signal-to-noise ratio (Boubela et al. 2015). Habituation of neurons within the amygdala constitutes potentially confounding factor and thus, should be carefully considered at all stages of the experiment, starting from planning and ending with data analysis and inference.

Finally, it should be stressed that in the light of recent findings on neuronal circuits regulating appetitive behavior, collecting and analysis of human neuroimaging data seem to be even more challenging. Specifically, animal research has shown that in the same amygdala subdivision different circuits that regulate opposite behaviors might exist (e.g. Knapska et al. 2012, Kim et al. 2016, 2017). For example, Kim and colleagues (2017) identified distinct populations of neurons within the CeA, which drive appetitive behavioral responding. One population of neurons receive input from the BLA *Ppp1r1b*⁺ neuronal cells, which can be characterized by their ability to induce reward-seeking behavior. Another population of neurons within the CeA receive input from the BLA *Rspo2*⁺ neurons, which was shown to inhibit appetitive responding (Kim et al. 2016). Altogether, the two pathways are suggested to form a BLA-to-CeA circuit for the antagonistic control of reward-related behavior. Such findings might partly explain contradictory results observed in human studies on functional organization of the amygdala in appetitive learning. Nonetheless, they also

suggest that more sensitive methods for collecting and analysis of human neuroimaging data will be needed.

Parcellation of the amygdala

Finally, the difficulty in examination of the functional organization of the human amygdala arises from the lack of the common and generally accepted method of parcellating this structure. The techniques used in animal studies, like single neuron recordings or *post mortem* staining allow for precise localization of the neural signal within the amygdala. Yet, the only non-invasive method of investigation of this subcortical structure in healthy subjects is fMRI, which apparently is not optimal for the purpose of differentiation between the activity in the individual amygdalar subregions due to insufficient spatial resolution (but see Davis et al. 2010). For this reason, there is a need to parcel the amygdala into subdivisions, which will correspond with its structural arrangement. To date, three approaches have been proposed: probabilistic maps, manual segmentation and connectivity-based parcellation.

Probabilistic maps of superficial, centromedial and laterobasal groups of nuclei were calculated by Amunts and others (2005). The authors performed 3D reconstruction of *post mortem* data. The histological analysis was carried out on ten human brains from subjects with average age of 65 years. In the final step they calculated probabilistic maps, which specify the probability with which each voxel within the amygdala belongs to each group of nuclei. Application of this technique is relatively easy and does not require considerable load of effort or time. Thus, it has been extensively used in research on the role of the amygdala subregions in facial emotion perception (Hurlemann et al. 2008, Barbour et al. 2010, Hortensius et al. 2016), auditory stimulation with pleasant and unpleasant music excerpts (Ball et al. 2007) and emotional voices (Frühholz and Grandjean 2013) or perceiving social cues (Freeman et al. 2014). However, as critically pointed by Prévost and colleagues (2011), the probabilistic maps might not be applicable for the studies with younger sample than the one used in the study by Amunts and colleagues due to extensive age-related changes in structure of the brain. In particular, changes in volume of the amygdala over time (Fjell et al. 2013, Pressman et al. 2016, for a review see Wright 2009) might be a reason for a mismatch between the location and size of the distinct groups of nuclei in younger and older adults.

An alternative approach is manual delineation of amygdalar subdivisions. This method was applied to clarify functions of the CMA and the BLA in reward and avoidance learning (Prévost et al. 2011) and in general and specific Pavlovian-to-instrumental transfer (Prévost et al. 2012). A detailed protocol for manual amygdala

parcellation was proposed by Entis and others (2012), who developed a procedure dependent on visual inspection of ultra-high resolution MRI scans guided with a histological atlas (Mai et al. 2008). Tracing of four amygdalar subregions (basolateral, basomedial, centromedial and amygdaloid cortical) was based on geometrical method. Although this approach provides more precise results than the probabilistic maps, it has several limitations. Firstly, the geometrically-delineated subregions are only approximation of the anatomical groups of amygdalar nuclei and any individual differences in nuclei shape cannot be taken into account. Secondly, one objective of parcellation of the amygdala is to create masks of individual subregions which will facilitate precise labelling of BOLD signal location during the mental task performance. Yet, due to long time of acquisition of ultra-high resolution data the method might be difficult to be used together with functional scanning. Lastly, manual tracing is time consuming method and, to a large degree, its reliability might rely on the experience of a rater.

Recently, methods of manual segmentation and probabilistic maps calculation have been combined to construct two new atlases of the human amygdala. Tyszka and Pauli (2016) used high resolution T1- and T2-weighted images from the Human Connectome Project to delineate 10 subdivisions of the amygdaloid complex, whereas Saygin and colleagues (2017) traced 9 nuclei based on the data from ultra-high-resolution *ex vivo* imaging of 10 autopsied brain hemispheres.

The third group of methods represents connectivity-driven approach. It takes advantage of the fact that the distinct nuclei of the amygdala have different patterns of connectivity with other brain regions. Available techniques allow to determine both, anatomical and functional connections.

In humans, anatomical projections can be visualized using diffusion tensor imaging (DTI). The rationale behind this technique is the phenomenon of varying diffusivity of water molecules across different tissues and brain structures (Bammer 2003). Heretofore, there are three studies, in which DTI-based parcellation of the human amygdala was performed. Solano-Castiella and colleagues (2010) proposed division into two parts, but their outcome is not in accord with present knowledge of amygdala structure. Another parcellation into two subregions was conducted by Bach and associates (2011), but probably the most accurate result was obtained by Saygin and others (2011), who differentiated four main subdivisions. Although there is solid motivation to use DTI for the purpose of amygdala parcellation, a few limitations need to be considered. Probably the major difficulty results from the assumption that within a single voxel populations of white matter tracts share the same orientation. Hence, in regions of crossing fibers much information might be lost

(Mori and Zhang 2006). Additionally, DTI remains time consuming in terms of analysis.

For these reasons, researchers are now interested in parcellation of the amygdala based on its functional connectivity with other brain regions. This can be achieved using resting-state fMRI (rsfMRI), which relies on analysis of spontaneous fluctuations in BOLD signal in the absence of an explicit task. High correlation of BOLD time series from two structures is interpreted as regional interaction (Fox and Raichle 2007). To date, two groups attempted to divide the amygdala using this technique. Mishra and colleagues (2014) demonstrated that rsfMRI may be a valuable tool serving separation of the amygdala into at least two parts comparable to the ones obtained by Bach and others (2011). Bielski and colleagues (2016) isolated four subdivision which corresponded to centromedial, cortical, basal and lateral groups of nuclei with respect to location, size and connectivity patterns. rsfMRI is a promising method and has the advantage over DTI-based parcellation, because it is quick in terms of data collection and analysis and is free from limitations such as crossing fibers.

CONCLUSIONS

There is no doubt that the amygdala plays an important role in appetitive learning. Since abnormalities in this process are associated with medical conditions, there is urgency to come up with new models of the human amygdala functioning which would take into account the anatomical diversity of this structure. Despite of extensive research in animals, there is no agreement on the functional organization of the amygdala. Some authors (e.g. Parkinson et al. 2000, Knapska et al. 2013) seem to emphasize the integrity of centromedial group of nuclei to be a pivotal factor of successful appetitive learning, but there is an alternative view which recognizes the importance of both complexes pointing the dissociable contribution of centromedial and basolateral groups of nuclei (e.g. Moscarello and LeDoux, 2013). Upon facing the fact that there is no reliable method to discriminate between activity in distinct amygdalar subregions, so far only few studies undertook the issue of functional organization of the human amygdala in context of appetitive learning. However, these studies were not able to verify which hypothesis formulated on the basis of animal research is more accurate. This lack of conclusive findings may be brought about several aspects. First of all, although primary rewards seem to be a more justified choice, in human studies secondary reinforcers like monetary gains are often selected. Secondly, neural response in the amygdala undergoes a rapid habituation, which hinders efforts to capture this transient activity. Finally, as already mentioned, there is no single acknowledged approach to divide the amygdala into

its anatomical subregions. As a result different research groups utilize an assortment of parcellation methods. Certainly, the produced outcomes cannot be compared with each other, since these parcellation methods vary substantially in terms of number of isolated subregions, their shape, size and localization. Consequently, a first step towards conclusive research design should be development of a method which could become a gold standard in parcellation of the amygdala. Further, planning of the experimental procedures and analysis of the results in accordance with the current knowledge of the modulatory impact of factors, some of which mentioned in this review, should bring in more reproducibility and conclusiveness in the research on functional organization of the human amygdala in appetitive learning.

ACKNOWLEDGEMENT

This work was supported by a grant from the Polish National Science Centre based on decision number DEC-2014/15/B/HS6/03658.

REFERENCES

- Aggleton JP, Passingham RE (1981) Syndrome produced by lesions of the amygdala in monkeys (*Macaca mulatta*). *J Comp Physiol Psychol* 95(6): 961–977.
- Amunts K, Kedo O, Kindler M, Pieperhoff P, Mohlberg H, Shah NJ, Habel U, Schneider F, Zilles K (2005) Cytoarchitectonic mapping of the human amygdala, hippocampal region and entorhinal cortex: intersubject variability and probability maps. *Anat Embryol (Berl)* 210(5–6): 343–352.
- Appenzeller S, Chaloult E, Velho P, de Souza EM, Araújo VZ, Cendes F, Li LM (2006) Amygdalae calcifications associated with disease duration in lipid proteinosis. *J Neuroimaging* 16(2): 154–156.
- Bach DR, Behrens TE, Garrido L, Weiskopf N, Dolan RJ (2011) Deep and superficial amygdala nuclei projections revealed in vivo by probabilistic tractography. *J Neurosci* 31(2): 618–623.
- Baeuchl C, Meyer P, Hoppstädter M, Diener C, Flor H (2015) Contextual fear conditioning in humans using feature-identical contexts. *Neurobiol Learn Mem* 121: 1–11.
- Ball T, Rahm B, Eickhoff SB, Schulze-Bonhage A, Speck O, Mutschler I (2007) Response properties of human amygdala subregions: evidence based on functional MRI combined with probabilistic anatomical maps. *PLoS One* 2(3): e307.
- Bammer R (2003) Basic principles of diffusion-weighted imaging. *Eur J Radiol* 45(3): 169–184.
- Barbour T, Murphy E, Pruitt P, Eickhoff SB, Keshavan MS, Rajan U, Zajac-Benitez C, Diwadkar VA (2010) Reduced intra-amygdala activity to positively valenced faces in adolescent schizophrenia offspring. *Schizophr Res* 123(2–3): 126–136.
- Barch DM, Burgess GC, Harms MP, Petersen SE, Schlaggar BL, Corbetta M, Glasser MF, Curtiss S, Dixit S, Feldt C, Nolan D, Bryant E, Hartley T, Footer O, Bjork JM, Poldrack R, Smith S, Johansen-Berg H, Snyder AZ, Van Essen DC, WU-Minn HCP Consortium (2013) Function in the human connectome: task-fMRI and individual differences in behavior. *Neuroimage* 80: 169–189.
- Baxter MG, Murray EA (2002) The amygdala and reward. *Nat Rev Neurosci* 3(7): 563–573.
- Bechara A, Tranel D, Damasio H, Adolphs R, Rockland C, Damasio AR (1995) Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans. *Science* 269(5227): 1115–1118.
- Bedny M, Aguirre GK, Thompson-Schill SL (2007) Item analysis in functional magnetic resonance imaging. *Neuroimage* 35(3): 1093–1102.
- Bielski K, Falkiewicz M, Kolada E, Szatkowska I (2016) Functional connectivity-based parcellation of the human amygdala using an fMRI data from the Human Connectome Project. A resting state approach. The Fifth Biennial Conference on Resting State and Brain Connectivity, September 21–23, Vienna, Austria. [http://www.restingstate.com/2016/abstracts/\(abstract n° 17\)](http://www.restingstate.com/2016/abstracts/(abstract%20n%2017)).
- Blackford JU, Buckholz JW, Avery SN, Zald DH (2010) A unique role for the human amygdala in novelty detection. *Neuroimage* 50(3): 1188–1193.
- Boubela RN, Kalcher K, Huf W, Seidel EM, Derntl B, Pezawas L, Našel C, Moser E (2015) fMRI measurements of amygdala activation are confounded by stimulus correlated signal fluctuation in nearby veins draining distant brain regions. *Sci Rep* 5: 10499.
- Braesicke K, Parkinson JA, Reekie Y, Man MS, Hopewell L, Pears A, Crofts H, Schnell CR, Roberts AC (2005) Autonomic arousal in an appetitive context in primates: a behavioural and neural analysis. *Eur J Neurosci* 21(6): 1733–1740.
- Cardinal RN, Parkinson JA, Hall J, Everitt BJ (2002) Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. *Neurosci Biobehav Rev* 26(3): 321–352.
- Carey RJ, Carrera MP, Damianopoulos EN (2014) A new proposal for drug conditioning with implications for drug addiction: the Pavlovian two-step from delay to trace conditioning. *Behav Brain Res* 275: 150–156.
- Corbit LH, Balleine BW (2005) Double dissociation of basolateral and central amygdala lesions on the general and outcome-specific forms of pavlovian-instrumental transfer. *J Neurosci* 25(4): 962–970.
- Cox SM, Andrade A, Johnsrude IS (2005) Learning to like: a role for human orbitofrontal cortex in conditioned reward. *J Neurosci* 25(10): 2733–2740.
- Cybulska-Klosowicz A (2016) Behavioral verification of associative learning in whiskers-related fear conditioning in mice. *Acta Neurobiol Exp (Wars)* 76(2): 87–97.
- Davis FC, Johnstone T, Mazzulla EC, Oler JA, Whalen PJ (2010) Regional response differences across the human amygdaloid complex during social conditioning. *Cereb Cortex* 20(3): 612–621.
- Davis M, Whalen PJ (2001) The amygdala: vigilance and emotion. *Mol Psychiatry* 6(1): 13–34.
- DiFeliceantonio AG, Berridge KC (2012) Which cue to 'want'? Opioid stimulation of central amygdala makes goal-trackers show stronger goal-tracking, just as sign-trackers show stronger sign-tracking. *Behav Brain Res* 230(2): 399–408.
- Donnet S, Lavielle M, Poline J-B (2006) Are fMRI event-related response constant in time? A model selection answer. *Neuroimage* 31(3): 1169–1176.
- Entis JJ, Doerga P, Barrett LF, Dickerson BC (2012) A reliable protocol for the manual segmentation of the human amygdala and its subregions using ultra-high resolution MRI. *Neuroimage* 60(2): 1226–1235.
- Everitt BJ, Cardinal RN, Parkinson JA, Robbins TW (2003) Appetitive behavior: impact of amygdala-dependent mechanisms of emotional learning. *Ann N Y Acad Sci* 985: 233–250.
- Everitt BJ, Dickinson A, Robbins TW (2001) The neuropsychological basis of addictive behaviour. *Brain Res Brain Res Rev* 36(2–3): 129–138.
- Fischer H, Wright CI, Whalen PJ, McInerney SC, Shin LM, Rauch SL (2003) Brain habituation during repeated exposure to fearful and neutral faces: a functional MRI study. *Brain Res Bull* 59(5): 387–392.
- Fjell AM, McEvoy L, Holland D, Dale AM, Walhovd KB, Alzheimer's Disease Neuroimaging Initiative (2013) Brain changes in older adults at very low risk for Alzheimer's disease. *J Neurosci* 33(19): 8237–8242.

- Fox MD, Raichle ME (2007) Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nat Rev Neurosci* 8(9): 700–711.
- Freeman JB, Stolier RM, Ingbreten ZA, Hehman EA (2014) Amygdala responsiveness to high-level social information from unseen faces. *J Neurosci* 34(32): 10573–10581.
- Freese JL, Amaral DG (2009) Neuroanatomy of the primate amygdala. In: *The Human Amygdala* (Whalen PJ, Phelps EA, Eds). The Guilford Press, New York, USA. p. 3–42.
- Frühholz S, Grandjean D (2013) Amygdala subregions differentially respond and rapidly adapt to threatening voices. *Cortex* 49(5): 1394–1403.
- Gaffan EA, Gaffan D, Harrison S (1988) Disconnection of the amygdala from visual association cortex impairs visual reward-association learning in monkeys. *J Neurosci* 8(9): 3144–3150.
- Gottfried JA, O'Doherty J, Dolan RJ (2002) Appetitive and aversive olfactory learning in humans studied using event-related functional magnetic resonance imaging. *J Neurosci* 22(24): 10829–10837.
- Gottfried JA, O'Doherty J, Dolan RJ (2003) Encoding predictive reward value in human amygdala and orbitofrontal cortex. *Science* 301(5636): 1104–1107.
- Holland PC, Hatfield T, Gallagher M (2001) Rats with basolateral amygdala lesions show normal increases in conditioned stimulus processing but reduced conditioned potentiation of eating. *Behav Neurosci* 115(4): 945–950.
- Hortensius R, Terburg D, Morgan B, Stein DJ, van Honk J, de Gelder B (2016) The role of the basolateral amygdala in the perception of faces in natural contexts. *Philos Trans R Soc Lond B Biol Sci* 371(1693): 20150376.
- Hurlemann R, Rehme AK, Diessel M, Kukulja J, Maier W, Walter H, Cohen MX (2008) Segregating intra-amygdalar responses to dynamic facial emotion with cytoarchitectonic maximum probability maps. *J Neurosci Methods* 172(1): 13–20.
- Izquierdo A, Murray EA (2007) Selective bilateral amygdala lesions in rhesus monkeys fail to disrupt object reversal learning. *J Neurosci* 27(5): 1054–1062.
- Kerr KL, Avery JA, Barcalow JC, Moseman SE, Bodurka J, Bellgowan PS, Simmons WK (2015) Trait impulsivity is related to ventral ACC and amygdala activity during primary reward anticipation. *Soc Cogn Affect Neurosci* 10(1): 36–42.
- Kim J, Pignatelli M, Xu S, Itoharu S, Tonegawa S (2016) Antagonistic negative and positive neurons of the basolateral amygdala. *Nat Neurosci* 19(12): 1636–1646.
- Kim J, Zhang X, Muralidhar S, LeBlanc SA, Tonegawa S (2017) Basolateral to central amygdala neural circuits for appetitive behaviors. *Neuron* 93(6): 1464–1479.
- Kirsch P, Schienle A, Stark R, Sammer G, Blecker C, Walter B, Ott U, Burkart J, Vaitl D (2003) Anticipation of reward in a nonaversive differential conditioning paradigm and the brain reward system: an event-related fMRI study. *Neuroimage* 20(2): 1086–1095.
- Klucken T, Wehrum S, Schweckendiek J, Merz CJ, Hennig J, Vaitl D, Stark R (2013) The 5-HTTLPR polymorphism is associated with altered hemodynamic responses during appetitive conditioning. *Hum Brain Mapp* 34(10): 2549–2560.
- Knapska E, Lioudyno V, Kiryk A, Mikosz M, Górkiewicz T, Michaluk P, Gawlak M, Chaturvedi M, Mochol G, Balcerzyk M, Wojcik DK, Wilczynski GM, Kaczmarek L (2013) Reward learning requires activity of matrix metalloproteinase-9 in the central amygdala. *J Neurosci* 33(36): 14591–14600.
- Knapska E, Macias M, Mikosz M, Nowak A, Owczarek D, Wawrzyniak M, Pieprzyk M, Cymerman IA, Werka T, Sheng M, Maren S, Jaworski J, Kaczmarek L (2012) Functional anatomy of neural circuits regulating fear and extinction. *Proc Natl Acad Sci U S A* 109(42): 17093–17098.
- Knapska E, Radwanska K, Werka T, Kaczmarek L (2007) Functional internal complexity of amygdala: focus on gene activity mapping after behavioral training and drugs of abuse. *Physiol Rev* 87(4): 1113–1173.
- Knapska E, Walasek G, Nikolaev E, Neuhäusser-Wespy F, Lipp HP, Kaczmarek L, Werka T (2006) Differential involvement of the central amygdala in appetitive versus aversive learning. *Learn Mem* 13(2): 192–200.
- László K, Kovács A, Zagoracz O, Ollmann T, Péczely L, Kertes E, Lacy DG, Lénárd L (2016) Positive reinforcing effect of oxytocin microinjection in the rat central nucleus of amygdala. *Behav Brain Res* 296: 279–285.
- Mahler SV, Berridge KC (2012) What and when to “want”? Amygdala-based focusing of incentive salience upon sugar and sex. *Psychopharmacol (Berl)* 221(3): 407–426.
- Mai JK, Paxinos G, Voss T (2008) *Atlas of the Human Brain*. Elsevier/Academic Press, San Diego, CA, USA.
- Málková L, Gaffan D, Murray EA (1997) Excitotoxic lesions of the amygdala fail to produce impairment in visual learning for auditory secondary reinforcement but interfere with reinforcer devaluation effects in rhesus monkeys. *J Neurosci* 17(15): 6011–6020.
- McDannald M, Kerfoot E, Gallagher M, Holland PC (2004) Amygdala central nucleus function is necessary for learning but not expression of conditioned visual orienting. *Eur J Neurosci* 20(1): 240–248.
- McDonald AJ (1998) Cortical pathways to the mammalian amygdala. *Prog Neurobiol* 55(3): 257–332.
- Metereau E, Dreher JC (2013) Cerebral correlates of salient prediction error for different rewards and punishments. *Cereb Cortex* 23(2): 477–487.
- Mishra A, Rogers BP, Chen LM, Gore JC (2014) Functional connectivity-based parcellation of amygdala using self-organized mapping: a data driven approach. *Hum Brain Mapp* 35(4): 1247–1260.
- Mori S, Zhang J (2006) Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron* 51(5): 527–539.
- Morris JS, Buchel C, Dolan RJ (2001) Parallel neural responses in amygdala subregions and sensory cortex during implicit fear conditioning. *Neuroimage* 13(6 Pt 1): 1044–1052.
- Moscarello JM, LeDoux JE (2013) The contribution of the amygdala to aversive and appetitive pavlovian processes. *Emotion Review* 5(3): 248–253.
- O'Doherty JP, Deichmann R, Critchley HD, Dolan RJ (2002) Neural responses during anticipation of a primary taste reward. *Neuron* 33(5): 815–826.
- Parkinson JA, Robbins TW, Everitt BJ (2000) Dissociable roles of the central and basolateral amygdala in appetitive emotional learning. *Eur J Neurosci* 12: 405–413.
- Paton JJ, Belova MA, Morrison SE, Salzman CD (2006) The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature* 439(7078): 865–870.
- Pessoa L (2010) Emotion and cognition and the amygdala: from “what is it?” to “what’s to be done?”. *Neuropsychologia* 48(12): 3416–3429.
- Pressman PS, Noniyeva Y, Bott N, Dutt S, Sturm V, Miller BL, Kramer JH (2016) Comparing volume loss in neuroanatomical regions of emotion versus regions of cognition in healthy aging. *PLoS One* 11(8): e0158187.
- Prévost C, Liljeholm M, Tyszka JM, O'Doherty JP (2012) Neural correlates of specific and general Pavlovian-to-Instrumental Transfer within human amygdalar subregions: a high-resolution fMRI study. *J Neurosci* 32(24): 8383–8390.
- Prévost C, McCabe JA, Jessup RK, Bossaerts P, O'Doherty JP (2011) Differentiable contributions of human amygdalar subregions in the computations underlying reward and avoidance learning. *Eur J Neurosci* 34(1): 134–145.
- Prévost C, McNamee D, Jessup RK, Bossaerts P, O'Doherty JP (2013) Evidence for model-based computations in the human amygdala during Pavlovian conditioning. *PLoS Comput Biol* 9(2): e1002918.
- Puschmann S, Brechmann A, Thiel CM (2013) Learning-dependent plasticity in human auditory cortex during appetitive operant conditioning. *Hum Brain Mapp* 34(11): 2841–2851.
- Quirk GJ, Armony JL, LeDoux JE (1997) Fear conditioning enhances different temporal components of tone-evoked spike trains in auditory cortex and lateral amygdala. *Neuron* 19(3): 613–624.

- Repa JC, Muller J, Apergis J, Desrochers TM, Zhou Y, LeDoux JE (2001) Two different lateral amygdala cell populations contribute to the initiation and storage of memory. *Nat Neurosci* 4(7): 724–731.
- Ross SE, Lehmann Levin E, Itoga CA, Schoen CB, Selmane R, Aldridge JW (2016) Deep brain stimulation in the central nucleus of the amygdala decreases 'wanting' and 'liking' of food rewards. *Eur J Neurosci* 44(7): 2431–2445.
- Sander D, Grafman J, Zalla T (2003) The human amygdala: an evolved system for relevance detection. *Rev Neurosci* 14(4): 303–316.
- Saygin ZM, Kliemann D, Iglesias JE, van der Kouwe AJW, Boyd E, Reuter M, Stevens A, Van Leemput K, McKee A, Frosch MP, Fischl B, Augustinack JC, Alzheimer's Disease Neuroimaging Initiative (2017) High-resolution magnetic resonance imaging reveals nuclei of the human amygdala: manual segmentation to automatic atlas. *Neuroimage* S1053–S8119(17): 30342–30347.
- Saygin ZM, Osher DE, Augustinack J, Fischl B, Gabrieli JD (2011) Connectivity-based segmentation of human amygdala nuclei using probabilistic tractography. *Neuroimage* 56(3): 1353–1361.
- Siebert M, Markowitsch HJ, Bartel P (2003) Amygdala, affect and cognition: evidence from 10 patients with Urbach-Wiethe disease. *Brain* 126(Pt 12): 2627–2637.
- Södersten P, Bergh C, Zandian M (2006) Understanding eating disorders. *Horm Behav* 50(4): 572–578.
- Solano-Castiella E, Anwender A, Lohmann G, Weiss M, Docherty C, Geyer S, Reimer E, Friederici AD, Turner R (2010) Diffusion tensor imaging segments the human amygdala in vivo. *Neuroimage* 49(4): 2958–2965.
- Spiegler B J, Mishkin M (1981) Evidence for the sequential participation of inferior temporal cortex and amygdala in the acquisition of stimulus-reward associations. *Behav Brain Res* 3(3): 303–317.
- Stefanacci L, Amaral DG (2002) Some observations on cortical inputs to the macaque monkey amygdala: an anterograde tracing study. *J Comp Neurol* 451(4): 301–323.
- Swanson LW, Petrovich GD (1998) What is the amygdala?. *Trends Neurosci* 21(8): 323–331.
- Tyszka JM, Pauli WM (2016) In vivo delineation of subdivisions of the human amygdaloid complex in a high-resolution group template. *Hum Brain Mapp* 37(11): 3979–3998.
- Valentin VV, Dickinson A, O'Doherty JP (2007) Determining the neural substrates of goal-directed learning in the human brain. *J Neurosci* 27(15): 4019–4026.
- Wedig MM, Rauch SL, Albert MS, Wright CI (2005) Differential amygdala habituation to neutral faces in young and elderly adults. *Neurosci Lett* 385(2): 114–119.
- Westfall J, Nichols T, Yarkoni T (2016) Fixing the stimulus-as-fixed-effect fallacy in task fMRI. *Wellcome Open Res* 1: 23.
- Whitton AE, Treadway MT, Pizzagalli DA (2015) Reward processing dysfunction in major depression, bipolar disorder and schizophrenia. *Curr Opin Psychiatry* 28(1): 7–12.
- Wright CI (2009) The human amygdala in normal aging and Alzheimer's disease. In: *The Human Amygdala* (Whalen PJ, Phelps EA, Eds). The Guilford Press, New York, USA. p. 382–405.
- Zald DH (2003) The human amygdala and the emotional evaluation of sensory stimuli. *Brain Res Brain Res Rev* 41(1): 88–123.