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The functional profile of the human amygdala in affective processing: Insights from intracranial recordings

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ABSTRACT

The amygdala is suggested to serve as a key structure in the emotional brain, implicated in diverse affective processes. Still, the bulk of existing neuroscientific investigations of the amygdala relies on conventional neuroimaging techniques such as fMRI, which are very useful but subject to limitations. These limitations are particular to their temporal resolution, but also to their spatial precision at a very fine-grained level. Here, we review studies investigating the functional profile of the human amygdala using intracranial electroencephalography (iEEG), an invasive technique with high temporal and spatial precision. We conducted a systematic literature review of 47 iEEG studies investigating the human amygdala, and we focus on two content-related domains and one process-related domain: (1) memory formation and retrieval; (2) affective processing; and (3) latency components. This review reveals the human amygdala to engage in invariant semantic encoding and recognition of specific objects and individuals, independent of context or visuospatial attributes, and to discriminate between familiar and novel stimuli. The review highlights the amygdala's role in emotion processing witnessed in differential treatment of social-affective facial cues, differential neuronal firing to relevant novel stimuli, and habituation to familiar affective stimuli. Overall, the review suggests the amygdala plays a key role in the processing of affective relevance. Finally, this review delineates effects on amygdala neuronal activity into three time latency windows (post-stimulus onset). The early window (~50–290 msec) subsumes effects respective to exogenous stimulus-driven affective processing of faces and emotion. The intermediate window (~270–470 msec) comprises effects related to explicit attention to novel task-relevant stimuli, irrespective of sensory modality. The late window (~600–1400 msec) subsumes effects from tasks soliciting semantic associations and working memory during affective processing. We juxtapose these iEEG data with current clinical topics relevant to amygdala activation and propose avenues for future investigation of the amygdala using iEEG methods.

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1. Introduction

Contemporary neuroscience literature illustrates the human amygdala to significantly contribute to the perception and memory consolidation of affectively relevant stimuli (Bechara et al., 1995; Brosch & Wieser, 2011; Cunningham & Brosch, 2012; Davis & Whalen, 2001; Holland & Gallagher, 1999; LeDoux, 2000; Sander, Grafman, & Zalla, 2003). However, the exact computational profile of the amygdala in affective processing is still a matter of debate. Intracranial electroencephalography (iEEG) measurements may, in fact, provide unique insight into amygdala neuronal processing of affective stimuli at the neuronal level. In our review of the iEEG literature, we delineate three overarching domains, two of which are content-related and one which is process-based. The first content-related domain discussed is memory formation and retrieval, wherein we highlight the amygdala's role in familiarity/novelty detection, selective encoding and recognition, familiarity and attention, and conscious awareness. The second content-related domain outlined is affective processing, where we highlight amygdala neuronal involvement in the processing of faces, fear, and arousal, as well as behavioral and motivational relevance. For the process-based domain, we discuss latency components wherein we disaggregate local field potentials of amygdala neuronal populations into three temporal components according to their early, intermediate, and late responses. Finally, in the discussion of our review, we juxtapose these domains with relevant clinical issues pertaining to anxiety-related and personality disorders.

Evidence from neuroimaging data and neuropsychological testing reveals great heterogeneity of amygdala responses, including emotion processing (Phelps & Anderson, 1997; Vuilleumier, 2005), face-processing (Vuilleumier, 2005; Whalen, 1998), voice processing (Andics et al., 2010; Fruhholz & Grandjean, 2013; Sander et al., 2005), arousal processing (Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000), novelty detection (Schwartz, Wright, Shin, Kagan, & Rauch, 2003; Zald, 2003), ambiguity resolution (Brand, Grabenhorst, Starcke, Vandekerckhove, & Markowitsch, 2007; Whalen, 1998), behavioral (Ousdal et al., 2008) and motivational (Cunningham & Brosch, 2012; Pessoa & Adolphs, 2010) relevance detection, and learning and memory consolidation (Hamann, 2009). This research may implicate a learning and memory consolidation by the human amygdala that is based on the emotional value or affective relevance imbued in the encoded event/object (Cunningham & Brosch, 2012; Sander et al., 2003). Notably, however, the majority of these findings relies on conventional neuroimaging techniques, such as functional or structural MRI or scalp EEG/MEG. Furthermore, the displayed heterogeneity evidenced in human amygdala functioning may speak to specific underlying processes that have yet to be reviewed in studies using complementary neuroimaging tools.

Conventional neuroscience evidence suggests that the amygdala selectively encodes emotional stimuli according to the degree of detected motivational relevance (Markowitsch & Staniloiu, 2011; Sander et al., 2003). Relevance describes a stimulus or experience that directly implicates the preservation of the self (Markowitsch & Staniloiu, 2011), whether it be survival (Conway & Pleydell-Pearce, 2000), basic needs satisfaction, goal-accomplishment, or affirmation of the conceptual and working self (Jobson, 2009). Relevance can include behavioral relevance (Ousdal et al., 2008) as well as motivational relevance (Cunningham & Brosch, 2012; Pessoa & Adolphs, 2010; Sander et al., 2003). To date, however, no extensive review has been conducted to determine the level to which amygdala activity, at the neuronal level, implicates relevance decoding in perceptual and memory processes. Given the superior spatial-temporal precision afforded by iEEG measurements, a review of the iEEG human amygdala literature may broaden our understanding of the computational profiles relevant to amygdala neuronal functioning.

Intracranial EEG techniques offer a unique opportunity to merge temporal and spatial precision into one single recording and can elucidate findings retrieved from conventional neuroscience methods. In the current review, therefore, we effectuated what was, to the best of our knowledge, an exhaustive search of the iEEG literature to retrieve all studies in which the human amygdala was included in the principle analyses, irrespective of the task. We collected a total of 47 studies employing iEEG techniques, assessing the human amygdala via single-neuron and intracranial local field potential (iLFP) recordings (see Table 1).

1.1. *Limitations of conventional neuroimaging methods*

Conventional human functional neuroimaging techniques are very useful to test many hypotheses but bear methodological limitations if relied upon alone. For instance, measuring blood oxygen level dependency (BOLD) via fMRI may require complementary analyses due to three technical setbacks: (1) differential sensitivity to increases of frequency bands of electrophysiological activity, particularly local field potential oscillations in the gamma range (Niessing et al., 2005), (2) smoothing and normalization which prohibit analyses at the neuronal level (Lindquist, 2008) and (3) slow temporal resolution (Dastjerdi et al., 2011; Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001; Pourtois, Spinelli, Seeck, & Vuilleumier, 2010), posing a challenge to analyses at the millisecond level (Kwong et al., 1992; Logothetis, 2003). As timing of effects remains a crucial question surrounding amygdala functionality (cf. Brosch & Wieser, 2011), employing neuroimaging measures with high temporal precision would be indispensable.

Two such measures, recognized for their superior temporal resolution, are EEG and MEG. These non-invasive methods capture the spatial aggregation of local-field potentials (LFPs) with a temporal resolution of milliseconds (msec) (Schnitzler & Gross, 2005). While limited spatial resolution in EEG/MEG processing is generally acknowledged (Krolak-Salmon, Henaff, Vighetto, Bertrand, & Mauguiere, 2004; Tsuchiya, Kawasaki, Oya, Howard, & Adolphs, 2008), it remains uncertain whether these techniques possess significant utility in accessing deep cortical tissue such as the amygdala (Hashiguchi et al., 2007; Mikuni et al., 1997; Papadelis, Poghosyan, Fenwick, & Ioannides, 2009); hence, the benefit of employing iEEG techniques.

Table 1 – List of reviewed studies and their corresponding methodological attributes.

N°	Reference	Hem	Amygdala location	Method	Total N° of patients	Total N° of neurons[b]/ electrodes recorded	General targeted domain	Task
1	Brázdil et al., 2002	L/R	N/A[a]	iLFP	7	N/A	Arousal Processing Behavioral Relevance	Go/Nogo
2	Cameron et al., 2001	L/R	N/A	Single-neuron	12	19	Selective Encoding & Recognition	Word-Pair Encoding and Retrieval
3	Cerf et al., 2010	L/R	N/A	Single-neuron	12	12	Familiarity & Attention	Enhancement of image amid perceptual competition
4	Dellacherie et al., 2009	L	Basolateral Nuclei	iLFP	1	N/A	Affective Processing	Judgment of consonant (pleasant) versus dissonant (unpleasant) musical chords
5	Fried et al., 1997	L/R	N/A	Single-neuron	9	22 (encoding) 11 (recognition)	Familiarity/Novelty Detection Face Processing Fear Processing	Encoding and recognition of emotional faces
6	Fried et al., 2002	L/R	Basolateral Nuclei	Single-neuron	20	46 (encoding) 35 (recognition)	Familiarity/Novelty Detection Face Processing	Encoding and recognition of emotional faces
7	Gelbard-Sagiv et al., 2008	N/A	N/A	Single-neuron	13	163	Selective Encoding & Recognition Conscious Awareness	Category-Specific Encoding of Video Clip Presentation
8	Halgren, Babb, & Crandall, 1977	L/R	Basolateral Nuclei	Single-neuron	18	116[c]	Familiarity/Novelty Detection	Active sniffing from odorous flask
9	Halgren, Babb & Rausch, et al., 1977	L/R	Basolateral Nuclei	Single-neuron	18	116	Familiarity/Novelty Detection	Active sniffing from odorous flask
10	Halgren et al., 1978	L	Basolateral Nuclei	Single-neuron	15	54	Memory Formation & Retrieval	Word/image encoding & recognition
11	Halgren et al., 1980	L/R	Basolateral Nuclei	iLFP	6	8	Familiarity/Novelty Detection	Auditory oddball task
12	Halgren et al., 1994	L/R	Basolateral Nuclei	iLFP	26	27	Familiarity/Novelty Detection	Face encoding & recognition
13	Heit et al., 1988	L/R	N/A	Single-neuron	10	6	Selective Encoding & Recognition	Word encoding & recognition
14	Howard et al., 2012	N/A	N/A	Single-neuron	4	27	Memory Formation & Retrieval	Continuous Recognition Memory Task
15	Ison et al., 2011	N/A	N/A	Single-neuron	31	N/A	Selective Encoding & Recognition	Encoding & recognition task using various pictures
16	Jenison et al., 2011	L/R	Basolateral Nuclei Basomedial Nuclei Centromedial Nuclei	Single-neuron	3	51	Motivational Relevance	Judgment preference
17	Jung et al., 2006	L/R	N/A	iLFP	9	N/A	Familiarity/Novelty Detection	Odor recognition
18	Kreiman et al., 2000a	L/R	Basolateral Nuclei	Single-neuron	11	149	Face Processing	Face recognition
19	Kreiman et al., 2000b	L/R	N/A	Single-neuron	9	89	Memory Formation & Retrieval	Imagine Previously Viewed Images
20	Kreiman et al., 2002	L/R	N/A	Single-neuron	14	172	Selective Encoding & Recognition	Subjective perception using flash suppression
21	Krolak-Salmon et al., 2004	L/R	Superficial Nuclei	iLFP	10	N/A	Familiarity/Novelty Detection Face Processing Fear Processing	Target detection with emotionally expressive faces
22	Meletti et al., 2012	L/R	Basolateral Nuclei	iLFP	4	N/A	Face Processing Fear Processing	Perception of isolated facial regions expressing emotions
23	Mormann et al., 2008	N/A	N/A	Single-neuron	35	947	Selective Encoding & Recognition	Identifying faces in presented images of individuals, landmarks, animals, and objects
24	Mormann et al., 2011	R	N/A	Single-neuron	41	489	Arousal Processing	Perception of persons, animals, landmarks and objects
25	Mukamel et al., 2010	L/R	N/A	Single-neuron	4	33	Behavioral Relevance	Execution and Observation of Facial Expressions and Various Actions

26	Naccache et al., 2005	L/R	Basolateral Nuclei	iLFP	3	10	Fear Processing Conscious Awareness	Subliminal processing of emotional words
27	Oya et al., 2002	L/R	N/A	Event-Related Band Power Change (ERBP)	4	N/A	Arousal Processing	Passive perception of stimuli related to threat & danger
28	Paz et al., 2010	N/A	N/A	Single-neuron	11	160	Memory Formation & Retrieval	Encoding and recognition of individuals, landmarks, animals, and objects
29	Pedreira et al., 2010	N/A	N/A	Single-Neuron	26	238	Memory Formation & Retrieval Arousal Processing Relevance	Repeated stimulus presentation—photos of celebrities and familiar individuals, landmark buildings, animals, and objects
30	Pourtois, Spinelli, et al., 2010	L	Lateral	iLFP	1	N/A	Face Processing Fear Processing	Face vs house perception
31	Pourtois, Vocat et al., 2010	L/R	Basolateral Nuclei	iLFP	2	N/A	Arousal Processing Behavioral Relevance	Nogo task with non-emotional stimuli
32	Quiroga et al., 2005	L/R	N/A	Single-neuron	8	N/A	Selective Encoding & Recognition	Identifying faces in presented images of individuals, landmarks, animals, and objects
33	Quiroga et al., 2007	L/R	N/A	Single-neuron	11	N/A	Selective Encoding & Recognition	Identifying faces in presented images of individuals, landmarks, animals, and objects
34	Quiroga et al., 2008	N/A	N/A	Single-neuron	5	84	Selective Encoding & Recognition Conscious Awareness	Backward masking of familiar/novel images varying in presentation time intervals (33–264 msec)
35	Quian Quiroga et al., 2009	N/A	N/A	Single-neuron	7	216	Selective Encoding & Recognition	Visual image, visual word, and auditory presentation of individuals, landmarks, animals, and objects
36	Reddy et al., 2006	N/A	N/A	Single-neuron	9	208	Familiarity & Attention	Change detection of preferred stimulus
37	Rutishauser, Mamelak, et al., 2006	L/R	N/A	Single-neuron	6	145	Familiarity/Novelty Detection	Encoding and recognition
38	Rutishauser et al., 2008	L/R	N/A	Single-neuron	8	194	Familiarity/Novelty Detection	Encoding & recognition task examining recognition vs recollection of various pictures
39	Rutishauser et al., 2010	L/R	N/A[a]	Single-neuron iLFP	9	185	Memory Formation & Retrieval	Encoding & recognition task using various pictures
40	Rutishauser et al., 2011	L/R	N/A	Single-neuron	7	157	Face Perception Fear Processing	Face perception presenting whole face, isolated eye, isolated mouth, along with bubbles masking technique
41	Sato et al., 2011a	L/R	Medial to Lateral	iLFP	6	60[d]	Face Processing	Perception of Isolated Eyes with both Directed and Averted Gaze
42	Sato et al., 2011b	L/R	N/A	iLFP	6	504–684[e]	Face Processing Fear Processing	Dummy Target Detection Task: Gender identification of Fearful, happy, and neutral faces
43	Sato et al., 2012	L/R	Lateral, medial, superficial	iLFP	6	72	Face Processing	Dummy Target Detection Task: Cross detection amongst neutral faces, house and mosaics
44	Steinmetz, 2009	L/R	N/A	Single-neuron	10	59	Selective Encoding & Recognition Familiarity & Attention	Attentional Shifting between Picture Identification Task and Game Play
45	Stapleton & Halgren, 1987	L/R	N/A	Single-neuron iLFP	14	N/A	Familiarity/Novelty Detection	Auditory Oddball Task (Patients counted the number of rare tones)
46	Viskontas et al., 2009	L/R	N/A	Single-neuron	16	794	Motivational Relevance	Identifying faces in presented individuals of varying relevance (close, experimenters, unknown) as well as neutral non-human images

(*continued on next page*)

Table 1 – (continued)

N°	Reference	Hem	Amygdala location	Method	Total N° of patients	Total N° of neurons[b]/ electrodes recorded	General targeted domain	Task
47	Willenbockel et al., 2012	L	N/A	iLFP	1	1	Conscious Awareness Face Processing	Subliminal processing of fearful and disgusted faces

Hem = Hemisphere; iLFP = Intracranial local field potential; N° = Number; N/A = Not available/applicable.
[a] In situ fMRI or sMRI scan.
[b] Consists of single units and multi-units.
[c] Epileptic symptom etiologies were attributed to various neurological pathologies including encephalitis, head injury, birth trauma, subdural hematoma, and meningitis.
[d] 6 electrodes implanted in each hemisphere of each patient, however, one electrode in each hemisphere was implanted in adjacent white matter structure.
[e] Patients received 84–114 electrodes.

1.2. iEEG

Intracranial electroencephalography (iEEG) is an invasive neuroimaging procedure that records local cortical/subcortical neural activity via intracerebral electrodes implanted within gray matter regions of the brain. The advantage of iEEG analysis endures in its superior temporal (Sato et al., 2011b) and spatial (Hashiguchi et al., 2007) resolution of ≥5 msec and between ~.05 mm–1 cm, respectively (Asano et al., 2005; Gray, Maldonado, Wilson, & McNaughton, 1995; Grover & Buchwald, 1970; Legatt, Arezzo, & Vaughan, 1980; Logothetis, 2002, 2003). Additionally, iEEG can record neurons within a "large anatomical field-of-view… and wide frequency bandwidth" (Tsuchiya et al., 2008, p. 2), ranging from low (e.g., delta, theta) to high (e.g., beta, gamma) frequency potentials at both the population and individual single-neuron level (Tsuchiya et al., 2008; Willenbockel, Lepore, Nguyen, Bouthillier, & Gosselin, 2012). Recording at the population level, iEEG records intracranial LFPs (iLFPs), which consist of "extracellularly-recorded voltage fluctuations in the membrane potentials of a local neuronal population" spanning several millimeters in diameter (Schnitzler & Gross, 2005, p. 286).

Single-neuron recordings confer exceptional spatial resolution, with extracellular single-neuron electrodes, or microelectrodes, generally bearing a recording radius of ~.05–.35 mm (or 50–350 μm) (Gray et al., 1995; Grover & Buchwald, 1970; Legatt et al., 1980; Logothetis, 2002, 2003). While boasting superior temporal accuracy, macroelectrodes used for iLFP analyses record collective neuronal activity with a slightly lower degree of spatial resolution of roughly 1 cm (Lachaux, Rudrauf, & Kahane, 2003; Menon et al., 1996; Sato et al., 2012). Intracranial EEG would thus provide an important means to study the spatial and temporal neural dynamics specific to psychological and behavioral processes within human medial limbic tissue, such as the amygdala.

2. Methods

2.1. Recruitment of studies

Studies were collected via specific search criteria on PubMed. Search criteria consisted of the following:

(("human amygdala"[title/abstract]) OR (amygdala[title/abstract]) or ("medial temporal"[title/abstract]) OR ("temporal lobe"[title/abstract])) and (("single neuron"[title/abstract]) OR ("single neurons"[title/abstract]) OR ("single-neuron"[title/abstract]) OR (intracerebral[title/abstract]) OR (intracranial[title/abstract])) NOT (monkeys[title/abstract]) NOT (monkey[title/abstract]) NOT (rodents[title/abstract]) NOT (hamster[title/abstract]) NOT (rodent[title/abstract]) NOT (mice[title/abstract]) NOT (mouse[title/abstract]) NOT (rats[title/abstract]) NOT (rat[title/abstract]) NOT (primate[title/abstract]) NOT (simian[title/abstract]) NOT (murine[title/abstract]) NOT ("intracranial volume"[title/abstract])

This yielded 1,354 initial responses.

2.2. Exclusion criteria

Studies were excluded if they were identified as belonging to one of the following categories:

1) Intracranial EEG studies investigating patients with lesioned amygdala (e.g., Babiloni et al., 2009)
2) Intracranial EEG studies investigating patients with comorbid psychopathology such as autism spectrum disorders (e.g., Rutishauser et al., 2013) or psychosis (e.g., Takeda, Inoue, Tottori, & Mihara, 2001)
3) Intracranial EEG studies targeting pathological tissue, or tissue prone to epileptic discharges (i.e., epileptogenic) (e.g., Hughes & Andy, 1979; Oehl, Schulze-Bonhage, Lanz, Brandt, & Altenmuller, 2012; Wilson, Babb, Halgren, Wang, & Crandall, 1984) in their analyses
4) Intracranial EEG studies using group contrasts within patient groups according to the location of their amygdala epileptic zone (e.g., Guillem, N'Kaoua, Rougier, & Claverie, 1998; Mari, Zelmann, Andrade-Valenca, Dubeau, & Gotman, 2012)
5) Intracranial EEG studies which analyzed amygdala functioning in relation to active epileptic discharges (e.g., Tassinari et al., 2005; Urrestarazu et al., 2006)
6) Intracranial EEG studies highlighting analytic techniques of medial temporal lobe (MTL) recording (e.g., Rutishauser, Schuman, & Mamelak, 2006)

Remaining articles were screened for matching inclusion criteria (e.g., iEEG, healthy patients, human amygdala), resulting in 27 studies to be included in the review. An additional 20 articles were further retrieved from "snowball" methods (i.e., using reference lists (Greenhalgh & Peacock, 2005)), key author searches and related article searches, in addition to helpful recommendations from our reviewers. If not noted otherwise in the review, the highlighted iEEG articles recruited patients with pharmacologically intractable epilepsy. Table 1 provides a detailed list of the reviewed studies.

In these studies, intracranial electrodes were not implanted in pathological tissue, or if they were used to localize epileptic foci, they were controlled to ensure no abnormal firing during interictal periods (e.g., Halgren, Babb, & Crandall, 1978, Halgren, Babb, Rausch, & Crandall, 1977, Halgren et al., 1980). Due to the specific scope of this review, we do not review findings relevant to adjacent MTL regions (e.g., hippocampus) which are often reported in light of amygdala iEEG data (e.g., Ison et al., 2011).

2.3. Structure of review

Our collection of 47 iEEG studies spans the last four decades. Two main content-related domains (*memory* and *affective processing*) and one process-related domain (*latency components*) have emerged and will form the structure of our review. The content-related clusters were not mutually exclusive of one another. In this review, we attempt to incorporate essential findings from each iEEG study into a succinct synopsis bearing on these three main domains. We discuss the findings in light of extant neuroimaging literature and clinical research. We conclude with our interpretations given the iEEG data reviewed and propose future avenues of research investigating human amygdala functioning.

2.4. Limitations of iEEG

Five important caveats should be first taken into consideration when interpreting iEEG data. First, iEEG participants generally belong to a clinical population suffering from pharmacologically intractable epilepsy and thus do not represent physically healthy participants. Second, iEEG analyses occur only under exceptional cases of rare medical diagnoses. Consequently, median sample size is roughly 9 observations per study (Table 1). Therefore, while iEEG analyses confer exceptional advantages by virtue of their temporal and spatial precision, low sample collection in iEEG studies is an important methodological limitation to equally consider. This caveat notwithstanding, low sample size iEEG studies are generally compensated for by robust block designs thereby augmenting their statistical power. Third, given the heterogeneity of analyses (iLFPs, single-neuron, time-frequency) and tasks, a meta-analysis is not currently feasible. Additionally, a significant number of studies provide neither the nuclei (e.g., basolateral, centromedial, superficial) nor hemisphere location of their electrodes within the amygdala. We, thus, attempt a systematic and exhaustive review of all iEEG studies conducted on the whole human amygdala and discuss amygdala anatomy where appropriate and possible. Fourth, iLFP analyses of the reviewed studies below may incur a degree of contamination due to spiking activity (Waldert, Lemon, & Kraskov, 2013). While this may be particular to the alpha frequency (~10 Hz), it is theoretically possible to observe influences of spiking activity in cortical iLFPs in other ranges such as theta, beta and gamma (Waldert et al., 2013). Finally, it is important to note that the recorded potentials of event-related potentials (ERPs) depend on the position of the electrode site and its referent electrode (Fabiani, Gratton, & Coles, 2000). As polarity depends on the referent electrode position, we must treat our generalizations with caution due to the spatial precision that iEEG studies demand. Moreover, by virtue of their spatial precision, iEEG studies do not provide extensive mapping of the human amygdala. We thus cannot preclude influences of additional psychological processes, unmentioned in this review, which may be instantiated in hitherto unexamined amygdala neural tissue. Nevertheless, single-neuron and iLFP studies provide an exceptional opportunity to investigate the spatial and temporal dynamics of the amygdala at the neuronal level. In the following section, we discuss these dynamics in relation to memory formation and retrieval.

3. Memory formation and retrieval

Memory formation is crucial for learning from novel relevant experiences (Rutishauser, Ross, Mamelak, & Schuman, 2010), and iEEG evidence has reliably illustrated the importance of amygdala neuronal activity in encoding, recognition and recall accuracy of objects and events (Gelbard-Sagiv, Mukamel, Harel, Malach, & Fried, 2008; Halgren et al., 1978;

Heit, Smith, & Halgren, 1988; Howard, Viskontas, Shankar, & Fried, 2012; Kreiman, Koch, & Fried, 2000b; Paz et al., 2010; Quian Quiroga, Kraskov, Koch, & Fried, 2009; Quiroga, Mukamel, Isham, Malach, & Fried, 2008, Quiroga, Reddy, Kreiman, Koch, & Fried, 2005; Rutishauser et al., 2010). Importantly, this occurs independently of sensory modality (Quian Quiroga et al., 2009). Single-neuron studies have associated image recall accuracy with select firing of amygdala neurons at initial viewing and recognition periods (Cameron, Yashar, Wilson, & Fried, 2001; Gelbard-Sagiv et al., 2008; Kreiman, Koch, & Fried, 2000a; Quian Quiroga et al., 2009; Quiroga, Reddy, Koch, & Fried, 2007, Quiroga et al., 2005). Time-frequency analyses also delineate significant increases of amygdala oscillations synchronized within the theta frequency (2–10 Hz) during subsequently remembered trials (Rutishauser et al., 2010). Both amygdala oscillatory activity and firing rates (FR) may thus contribute to memory formation.

If the amygdala facilitates memory formation, it may respond differentially to specific properties, including the taxonomical or semantic/conceptual features of specific stimuli. IEEG evidence supports a selective object-based and category-based neural encoding. For instance, categories (e.g., animals) and specific objects (e.g., individuals) are shown to yield selective amygdala neuronal FR at encoding and recognition irrespective of presentation context and angular configurations (Gelbard-Sagiv et al., 2008; Kreiman, Fried, & Koch, 2002; Mormann et al., 2011; Quian Quiroga et al., 2009; Quiroga et al., 2005). Consequently, the amygdala may be removed from encoding contextual aspects relevant to the experienced stimulus, including temporal relationships of events and objects (Howard et al., 2012; Paz et al., 2010), spatial location of the respective stimulus (Rutishauser, Mamelak, & Schuman, 2006, Rutishauser, Schuman, & Mamelak, 2008), and even affectively neutral associative relationships (Cameron et al., 2001). Single-neuron studies by Howard et al. (2012) and Paz et al. (2010) both failed to show significant amygdala neural responding that would be indicative of temporal order processing of experienced events. Furthermore, Rutishauser, Mamelak, et al. (2006) and Rutishauser et al. (2008) observed amygdala neurons to discriminate familiar vs. novel stimuli with negligible amygdala neuron spiking activity when recalling the spatial location of the preferred stimulus 24 h post-stimulus presentation. Lastly, Cameron et al. (2001) showed no relation between amygdala FR and retrieval of associated words in a word-pair retrieval task, thus presenting no evidence for associative learning for neutral and otherwise semantically dissociable words. These results suggest that while amygdala neurons appropriate resources to memory formation, they may remain dissociated from long-term contextual encoding.

In further support of this claim, iEEG evidence suggests human amygdala neurons encode events in dissociated segments, organized individually according to category-based or object-based stimulus features (Gelbard-Sagiv et al., 2008; Kreiman et al., 2000a; Paz et al., 2010; Quiroga et al., 2007, 2005) and semantic/affective meaning (Naccache et al., 2005; Pedreira et al., 2010; Quian Quiroga et al., 2009). Several single-neuron studies illustrate the amygdala's capacity to selectively encode object categories (Gelbard-Sagiv et al., 2008; Kreiman et al., 2002, 2000a; Mormann et al., 2008; Pourtois, Spinelli, et al., 2010), individual objects (Kreiman et al., 2002; Quiroga et al., 2005, Quian Quiroga et al., 2009), and abstract concepts/images from words (Brázdil et al., 2002; Cameron et al., 2001; Halgren, Babb & Rausch, et al., 1977; Heit et al., 1988; Naccache et al., 2005). Thus, the amygdala may facilitate memory formation via select object-based/category-based encoding rather than contextualizing events in their temporal, spatial and associative context post 24 h. As will be discussed in the following subsection, a core purpose of this seemingly fragmented encoding may serve to distinguish familiar from novel and potentially relevant events (Gray et al., 1995; Rutishauser et al., 2010), thus suggesting potential appraisal mechanisms linked with novelty-familiarity concepts.

3.1. *Familiarity/novelty detection*

In two single-neuron studies, amygdala neuron spiking activity discriminated between familiar and novel stimuli but showed no differential spiking activity to 'contextually recollected' images after 24 h of initial viewing (Rutishauser, Mamelak, et al., 2006, 2008). Context was operationalized via the spatial location at which each respective image was presented (Rutishauser, Mamelak, et al. (2006); Rutishauser et al., 2008). Interestingly, amygdala neurons exhibited familiarity detection after only one initial encoding trial (Rutishauser, Mamelak, et al., 2006). As the authors proposed, this efficient synaptic plasticity of the amygdala may be adaptive for the organism to efficiently encode new and relevant information (Rutishauser, Mamelak, et al., 2006) rather than to place it in a contextual setting. Critically, neuronal firing discriminated between recollected (i.e., contextualized) and recognized (i.e., familiar) stimuli only 30 min after initial viewing. After 24 h, however, amygdala neuronal spiking activity discriminated only between recognized (familiar) and novel stimuli, suggesting an immediate role only for amygdala contextual encoding. Accordingly, the human amygdala may be less involved in constructing episodic memories (Cameron et al., 2001; Zola-Morgan & Squire, 1985; Zola-Morgan, Squire, & Amaral, 1989; Zola-Morgan, Squire, Amaral, & Suzuki, 1989) and more involved in constructing semantic representations of familiarity to discriminate between experienced and non-experienced events.

Familiarity detection may operate in parallel with novelty detection, possibly recruiting separate neural networks. Intracranial studies show the amygdala elicits differential amplitude to unfamiliar, relative to familiar, faces (Halgren et al., 1994), words (Halgren et al., 1994) and odors (Jung et al., 2006), suggesting a novelty detection function occurring irrespectively of sensory modality. Halgren et al. (1994) observed evidence of dual mechanisms facilitating familiarity and novelty detection. When patients explicitly attended to the valence and intensity of emotional expressions and words, the amygdala produced significantly greater iLFP amplitudes to novel faces and words at earlier latencies (~290 and ~470 msec post-stimulus onset (PSO)) and greater amplitude to familiar faces and words significantly later (~660 msec PSO) (Table 3) (Halgren et al., 1994), suggesting temporally dissociable mechanisms treating novel and familiar stimuli.

Furthermore, authors of a single-neuron study demonstrated separate neuronal populations firing selectively for either familiar or novel images and thus labeled these neurons "familiarity detectors" and "novelty detectors", respectively (Rutishauser, Mamelak, et al., 2006, p. 806). Moreover, they highlighted that this familiarity detection represents single-trial learning indicative of rapid synaptic plasticity that may be necessary for adaptive familiarity-novelty discrimination (Rutishauser, Mamelak, et al., 2006). Familiarity detection was further observed in an additional visual learning task by Rutishauser et al. (2008), wherein amygdala neurons showed mutually exclusive firing during the recognition session to familiar versus recollected (i.e., contextually accurate) memories whereby specific neurons exhibited elevated neuronal firing when correctly recollecting images than when recognizing them only. Together, these studies show that the amygdala may contribute to separate neural networks in detecting familiarity and novelty, irrespective of sensory modality.

Familiarity detection, however, may be more pronounced for affectively relevant stimuli (Fried, Cameron, Yashar, Fong, & Morrow, 2002, Fried, MacDonald, & Wilson, 1997; Krolak-Salmon et al., 2004). Single-neuron and iLFP data converge, demonstrating differential amygdala habituation to motivationally relevant stimuli in paradigms where preferred stimuli are interwoven with non-preferred stimuli between encoding and recognition periods. In a single-neuron study, Fried et al. (2002) observed significantly less amygdala spiking activity to familiar faces than familiar objects during recognition phase while the inverse was true when initially presenting all stimuli during encoding phase (i.e., more spiking activity to novel faces than to novel objects). Greater habituation to faces than neutral objects signals a facilitated habituation to biologically significant stimuli. During face perception alone, Krolak-Salmon et al. (2004) observed differential reduction in amygdala iLFP amplitude to familiar fearful, relative to familiar neutral, faces. Similarly, Fried et al. (1997) observed differential amygdala activity to emotion expression during recognition, but only in conjunction with stimulus novelty (i.e., whether the face was familiar or not). This lends further support to the explanation that the human amygdala facilitates affective relevance encoding and recognition.

In the context of immediate stimulus repetition, however, the amygdala may nonetheless habituate to neutral stimuli. Jung et al. (2006) demonstrated attenuated amygdala oscillations after paired exposure of neutral odors roughly 30 sec after initial presentation (Jung et al., 2006). Authors considered unlikely any parasitic influence from sensory adaptation mechanisms (cf. Jehl, Royet, & Holley, 1994) but did not preclude the influence of attentional factors. These findings are in light of earlier iEEG evidence illustrating the amygdala to yield increased and statistically equal neural activity to initial odors and air (Halgren, Babb, & Crandall, 1977, Halgren, Babb, & Rausch, et al., 1977). Thus, while novelty processing of 'neutral' odor may elicit no differential amygdala neuronal activity relative to air, amygdala neurons may nonetheless habituate rapidly to a neutral stimulus when it is immediately repeated. Nevertheless, iEEG evidence suggests underlying familiarity detection mechanisms and neural habituation to affectively relevant objects.

3.2. *Selective encoding and recognition*

In order to detect familiarity, the human amygdala may rely on stored schemas of specific attributes relevant to the preferred object. Discriminating familiar from unfamiliar entities in the environment would require the usage of stored mental representations, irrespective of the contextual conditions. This is demonstrated in two human amygdala single-neuron studies which observed invariant responding to specific objects and people regardless of the visual or auditory modality in which the image or name, respectively, was presented (Quian Quiroga et al., 2009; Quiroga et al., 2005). This representation may require the selective encoding of physical properties for individual objects, like facial characteristics of human beings. Such physical properties were shown to elicit selective, invariant, amygdala neuron spiking activity at encoding and retrieval (e.g., Gelbard-Sagiv et al., 2008; Kreiman et al., 2002) as well as free recall (Gelbard-Sagiv et al., 2008; Kreiman et al., 2000b). Interestingly, neuronal firing may be more selective in amygdala pyramidal cells than amygdala interneurons as illustrated by a single-neuron study (Ison et al., 2011). Nonetheless, selective neural responses suggest that the human amygdala encodes and retrieves object-based representations from one's environment.

Additional evidence indicates this encoding may relate to semantic learning and appraisal. Human amygdala neuronal firing is shown not only to be object-based but also category-based, preferring animals, landmarks or people (e.g., Kreiman et al., 2002; Kreiman et al., 2000a; Mormann et al., 2008; Quian Quiroga et al., 2009; Quiroga et al., 2008, 2005; Reddy, Quiroga, Wilken, Koch, & Fried, 2006; Steinmetz, 2009), and this encoding can occur within different sensory modalities, such as auditory and visual domains. Several single-neuron studies present evidence of semantic learning and recognition where selective amygdala spiking activity at encoding and retrieval emerged for words describing concepts or specific objects (Cameron et al., 2001; Heit et al., 1988; Naccache et al., 2005) or words describing previously viewed images (Quian Quiroga et al., 2009). Heit et al. (1988) showed that two-thirds of their recorded amygdala neurons preferentially fired during encoding and recognition for specific words (Table 2), which included abstract concepts (e.g., "luck") and verbs (e.g., "carve") (Heit et al., 1988). Quian Quiroga et al. (2009) illustrated that of the 216 amygdala neurons recorded, 14% invariantly responded to a visual image of an object or person as well as the written and spoken name of the preferred object/person (Table 2), signaling amygdala involvement in selective semantic association of familiar stimuli across various modality inputs. Finally, Cameron et al. (2001) delineated amygdala semantic processing from contextual associative processing. These authors showed that while amygdala FR correlated with familiar word retrieval alone, no correlation existed with the ability to retrieve the associated paired word. This would reflect an absence of associative pairing and the presence of verbal competency in retrieving familiar words (Cameron et al., 2001). Also important to consider is that amygdala baseline FR may influence neuronal selectivity, as was observed by Mormann et al. (2008). Results from this study yielded a significant inverse relationship with baseline neuronal FR for all selective

Table 2 – Studies and findings from single-neuron recordings.

N°	Reference	Hem effect	Amygdala location	Method	Condition	Total N° neurons active	%	Total N° of neurons recorded
1	Cameron et al., 2001	L/R	N/A	Single-Neuron	Encoding Only	3[a]	15.8%	19
					Retrieval Only	3[a]	15.8%	
					Both Encoding & Retrieval	4[a]	21.5%	
					Task Phase (Encoding/Retrieval)	2	10.5%	
					Recall Success	2	10.5%	
					Pair Type (Related/Unrelated)	1	5.3%	
2	Cerf et al., 2010	L/R	N/A	Single-Neuron	Attentional Competition Processing	N/A	N/A	12
3	Fried et al., 1997	L/R	N/A	Single-Neuron	Face Encoding	3	13.6%	22
					Face Recognition	3	27.3%	11
4	Fried et al., 2002	L/R	Basolateral Nuclei	Single-Neuron	Face Encoding	13	28.3%	46
					Face Recognition	4	11.4%	35
5	Gelbard-Sagiv et al., 2008	N/A	N/A	Single-Neuron	Response to Clip Presentation	95	58.3%	163
					Sustained Response to Clip Presentation	14	8.6%	95
6	Halgren, Babb, & Crandall, 1977	L/R	Basolateral Nuclei	Single-Neuron	Sniffing from Odorous Flask	~23	~20.0%	116
					Sniffing from Empty Flask	~23	~20.0%	116
7	Halgren, Babb & Rausch, et al., 1977	L/R	Basolateral Nuclei	Single-Neuron	Sniffing from Odorous Flask	~23	~20.0%	116
					Sniffing from Empty Flask	~23	~20.0%	116
8	Halgren et al., 1978	L	Basolateral Nuclei	Single-Neuron	Registration and coding of visual stimulus	2	3.7%	54
9	Heit et al., 1988	L/R	N/A	Single-Neuron	Word Selective	4	66.7%	6
10	Howard et al., 2012	N/A	N/A	Single-Neuron	Single-unit autocorrelation representing temporal context	3[b]	11.1%	27
11	Ison et al., 2011	N/A	N/A	Single-Neuron	Identifying a Person among images of people, landmarks, animals and objects	N/A	N/A	N/A
12	Jenison et al., 2011	L/R	Basolateral Nuclei Basomedial Nuclei Centromedial Nuclei	Single-Neuron	Preference Choice Processing	11	21.6%	51
					Preference Choice Processing	5	9.8%	
13	Kreiman et al., 2000a	L/R	Basolateral Nuclei	Single-Neuron	Visual stimuli processing	18	12.1%	149
					Category- or image-selective	14	9.4%	
					Face Selective	3.6[c]	2.4%	
14	Kreiman et al., 2000b	L/R	N/A	Single-Neuron	Visual Responsive	12	13.4%	89
					Visual Selective	9	10.1%	
					Imagery Responsive	8	9.0%	
					Imagery Selective	4	4.4%	
					Both Selective	3	3.4%	
15	Kreiman et al., 2002	L/R	N/A	Single-Neuron	Category- or image-selective	25	14.5%	172
					Flash Suppression	0	.0%	25
16	Mormann et al., 2008	N/A	N/A	Single-Neuron	Object-based selective encoding	101	10.7%	947
17	Mormann et al., 2011	R	N/A	Single-Neuron	Animal-selective Processing	35	7.2%	489
18	Mukamel et al., 2010	L/R	N/A	Single-Neuron	Action-Execution Only	11	33.3%	33
					Action-Observation Only	4	12.1%	
					Both Observation and Execution of Same Action Type	2[b]	6.1%	
					Observation/Execution Non-Match	1[b]	3.0%	

19	Paz et al., 2010	N/A	N/A	Single-Neuron	Neuronal activity correlating with video clip repetition	77	48.1%	160
					Neurons Exceeding Context-Independent Relationship	24	15.0%	
					Neurons Exceeding Pure-Stimulus Relationship	37	23.1%	
20	Pedreira et al., 2010	N/A	N/A	Single-Neuron	Mean Spike Number for Initial Trial (T1)	>.70	N/A	238
					Mean Spike Number for Last Trial (T6)	<.60		
21	Quiroga et al., 2005	L/R	N/A	Single-Neuron	Image Processing	30	N/A	N/A
					Invariant Image-Selective Processing	8		
22	Quiroga et al., 2007	L/R	N/A	Single-Neuron	Predictive Recognition during Encoding Processing	N/A	N/A	N/A
23	Quiroga et al., 2008	N/A	N/A	Single-Neuron	Stimulus presentation (33–264 msec)	4	4.8%	84
24	Quian Quiroga et al., 2009	N/A	N/A	Single-Neuron	Processing of at least one modality (visual image, visual word, and auditory presentation)	22	10.2%	216
					Multimodal Double Invariance[d]	4	18.2%	22
					Multimodal Triple Invariance[e] (visual image, visual word, and auditory presentation)	3	13.6%	
25	Reddy et al., 2006	N/A	N/A	Single-Neuron	Change Detection from Previously Encoded Objects	6	2.9%	208
26	Rutishauser et al., 2006a	L/R	N/A	Single-Neuron	Novelty or Familiarity Detection	12	8.3%	145
27	Rutishauser et al., 2008	L/R	N/A	Single-Neuron	Novelty Detection	30	15.5%	194
					Familiarity Detection	13	6.7%	
28	Rutishauser et al., 2011	L/R	N/A	Single-Neuron	Whole Face-Selective	32	20.4%	157
29	Steinmetz, 2009	L/R	N/A	Single-Neuron	Category-Selective Response during Picture Identification	11	18.6%	59
					Category-Selective Response during Game Play	10	16.9%	
					Category-Selective Response during Picture Identification & Game Play	8	80.0%	10
30	Viskontas et al., 2009	L/R	N/A	Single-Neuron	Identification of Self-Relevant Faces	52	6.5%	794

Hem = Hemispheric; N° = Number; N/A = Not available/applicable.

[a] Includes significant decreases in neuronal response in comparison to baseline.

[b] Results are not significantly greater than chance levels of 95% (i.e., $p < .05$).

[c] Decimal is derived from authors reporting 20% of visual stimuli processing neurons ($n = 18$ visual stimuli processing neurons, $N = 149$ total amygdala neurons measured) to be face-selective.

[d] Following the authors' definition of triple invariance, 'multimodal double invariance' in this context signifies neurons which fired invariantly for two of the three modalities (visual image, visual word, auditory presentation) (Quian Quiroga et al., 2009).

[e] Authors define "multimodal triple invariance" as neurons having "visual invariance together with significant responses to the spoken and written names of the same person or object." (Quian Quiroga et al., 2009, p. 1309).

Table 3 – Studies and findings from intracranial local field potential (iLFP) recordings.

N°	Reference	Hem effect	Amygdala location	Method	Condition	Time-frequency*	Component	Time of effects (Msec)
1	Brázdil et al., 2002	L/R	N/A	iLFP	Error Response	N/A	N1	122
					Error Response		P1	350
2	Dellacherie et al., 2009	L	Basolateral Nuclei	iLFP	Musical Dissonance Processing	N/A	Slow Wave	1200–1400
3	Halgren et al., 1980	L/R	Basolateral Nuclei	iLFP	Explicit Attention (Sounds)	N/A	P3	265–430
4	Halgren et al., 1994	L/R	Basolateral Nuclei	iLFP	New (*vs* Old) Face Processing	N/A	N310	287
							N430	468
					New (*vs* Old) Word Processing		N310	310
							N430	486
					Old (*vs* New) Face Processing		P630	662
					Old (*vs* New) Word Processing		P630	668
5	Jung et al., 2006	L/R	N/A	iLFP	New Odor Processing	Low Gamma (25–35 Hz)	N/A	349
6	Krolak-Salmon et al., 2004	L/R	Superficial Nuclei	iLFP	Attention to Emotion of Faces (explicit)	N/A	N200/N300	200–800
							Slow Wave	
					Attention to Gender of Faces (implicit)		Slow Wave	600–800
7	Meletti et al., 2012	L/R	Basolateral Nuclei	iLFP	Eye-Selective Processing	N/A	N/A	200–400
					Fearful Eye-Selective Processing	Theta (4–7 Hz)		200–500
8	Naccache et al., 2005	L/R	Basolateral Nuclei	iLFP	Subconscious Processing of Threatening Words	N/A	N/A	870
9	Oya et al., 2002	L/R	N/A	ERBP Change	Unpleasant (*vs* Pleasant) Stimuli Processing	Low Gamma (20–34 Hz)	N/A	50–150
								150–250
						High Gamma (36–60 Hz)		150–250
								350–450
10	Pourtois, Spinelli, et al., 2010	L	Lateral	iLFP	Fearful (*vs* Neutral) Face Processing	N/A	N200	140–290
					Explicit (*vs* Implicit) Attention toward Fearful & Neutral Faces		Slow wave	710
11	Pourtois, Vocat, et al., 2010	L/R	Basolateral Nuclei	iLFP	Slow Hits (Correct)	N/A	N/A	25
						Theta (<4 Hz)		−100–50[b]
					Fast Hits (Correct)	N/A		96
						Theta (<4 Hz)		−50–100[b]
					Active Error Response	N/A		320
						Theta (<4 Hz)		100–250[b]
12	Rutishauser et al., 2010	L/R	N/A	Single-Neuron iLFP	Predictive Recognition during Encoding Processing	Theta (2–10 Hz)	N/A	500
13	Sato et al., 2011a	L/R	Medial-Lateral	iLFP	Eye (*vs* Mosaic) Processing	Gamma (44 Hz)	N/A	200
14	Sato et al., 2011b	L/R	N/A	iLFP	Attention to Gender of Fearful (*vs* Neutral) Faces (implicit)	Gamma (38 Hz)	N/A	50–150
15	Sato et al., 2012	L/R	Lateral	iLFP	Face (*vs* Mosaic or House) Processing	Gamma (45–63 Hz)	N/A	200–300
16	Stapleton & Halgren, 1987	R	N/A	iLFP	Rare (*vs* Frequent) Sound Processing (explicit)	N/A	N2	200
							P3	300–400
17	Willenbockel et al., 2012	L	N/A	iLFP	Visible Emotional Face Processing	6.48 CPF[a]	N/A	240
					Invisible Emotional Face Processing	5.51 CPF[a]		140

CPF = cycles per face; ERBP = Event-Related Band Power; Hem = Hemispheric; iLFP = Intracranial local field potential; N° = Number; N/A = Not available/applicable.

*Column displays amygdala oscillatory responses wherein mean peak frequency difference is statistically significant (i.e., $p < .05$).

[a] Figures represent spatial-frequency threshold characteristics significantly activating amygdala neurons.

[b] Time-frequency band increases are relative to motor execution.

amygdala neurons, suggesting that lower baseline neuronal FR may precede, or even facilitate, higher selectivity. Taken together, these above-mentioned studies suggest specific amygdala neurons rely on semantic representations to perform object-based/category-based encoding and recognition, irrespective of sensory modality and presentation condition. Thus, amygdala encoding/recognition may rely on hierarchical semantic representations to ascribe the encoded event or stimulus to a taxonomical profile, which may facilitate familiarity detection.

3.3. *Familiarity and attention*

Familiarity detection, however, may be influenced by the allocation of attentional resources. In a single-neuron study, Cerf et al. (2010) demonstrated that amygdala spiking activity could be elicited by effectuating attentional strategies in order to enhance one preferred visual stimulus at the expense of another which was superimposed on the familiar preferred image. The selective neuron which fired initially for the preferred stimulus fired significantly above chance levels when the patient voluntarily enhanced the target stimulus, thereby attenuating the non-target image. These findings demonstrate that cognitive processes specific to willful attentional focus can override distracting and competing sensory input and directly influence neuronal firing within the amygdala (Cerf et al., 2010).

When attention is diverted away from the preferred stimulus, however, amygdala neurons appear unaffected by physical changes to the preferred stimulus (Reddy et al., 2006). Reddy et al. (2006) demonstrated that amygdala neuronal selective firing during initial viewing of various images predicted the accuracy of detecting change within a preferred stimulus during subsequent presentations, but only when the patient's attention was directed toward the preferred stimulus. Conversely, when the patient's attention was averted away from the preferred stimulus, stimulus change elicited no selective amygdala neuronal firing, thus signaling a "change blindness" of selective amygdala neurons (Reddy et al., 2006). Furthermore, these selective neurons fired only when change was detected but not when change was undetected, indicating that detected qualitative changes to familiar stimuli may elicit selective amygdala neuronal firing but only when attention is directed to such change (Reddy et al., 2006).

While amygdala neurons may be susceptible to "change blindness," they may nonetheless remain responsive to the appearance of the preferred stimulus alone, regardless of attentional factors. Explicitly, additional iEEG evidence suggests that selective amygdala neurons retain their reactivity to their preferred stimulus' presence despite averted attention. When involved in game-play, selective amygdala neurons still fired differentially to their preferred stimulus when it was presented in the background and thus when attention was directed toward and averted away from the preferred stimulus (Steinmetz, 2009). Taken together, these abovementioned studies suggest that provided that familiar stimuli undergo no explicit qualitative changes subsequent to initial encoding, selective amygdala neuronal firing may still remain responsive to any perceptible appearance of the preferred stimuli that remains above conscious thresholds, irrespective of attentional factors. Still, future research warrants complementary designs that further investigate the relation between preferred object recognition, attentional load, and conscious awareness, the latter demonstrating an intricate relation with amygdala neuronal firing and familiarity detection (cf. Kreiman et al., 2002; Quiroga et al., 2008).

3.4. *Conscious awareness*

Selective amygdala neurons are evidenced to give rise to conscious awareness of recognized familiar stimuli (Quiroga et al., 2008). In a single-neuron study, Quiroga et al. (2008) illustrated that patients' conscious awareness of stimulus familiarity depended not on presentation duration but rather on the firing of selective amygdala neurons. Authors used a backward masking technique to present familiar and novel images at varying time intervals, 33–264 msec in range. Stimuli included people (e.g., famous and close others), landmarks and animals (Quiroga et al., 2008). Thus, while stimulus presentation duration may still play a role in the conscious awareness of a familiar object, familiarity recognition appears to be ultimately linked to selective amygdala neuronal firing to the preferred stimulus. This is supported by an additional single-neuron study which showed that free recall of previously viewed images depends on amygdala neuronal firing milliseconds before the actual act of vocally recalling the memory (Gelbard-Sagiv et al., 2008). These findings suggest a contingency of conscious perception on the neuronal firing of selectively encoded amygdala neurons during familiar stimulus recognition and recall.

Still, a reciprocal relation may exist between amygdala neuronal firing and conscious familiar stimuli recognition. Single-neuron data show that selective amygdala neuronal reactivity is equally obstructed when familiar stimuli appear below conscious thresholds. Using a flash suppression technique wherein a novel non-preferred object is flashed in one eye (i.e., monocularly), rendering the preferred object imperceptible at conscious thresholds in the other eye, Kreiman et al. (2002) demonstrated no amygdala neuronal firing to the flash suppression of the preferred object (Table 2). Thus, subjective phenomenal perception of familiar stimuli may be suppressed when conscious awareness is diverted to the flashed unrelated stimulus thereby dampening amygdala neuron FR to below significance levels (Kreiman et al., 2002). Critically, however, this may be specific to familiar neutral stimuli as both Willenbockel et al. (2012) and Naccache et al. (2005) witnessed amygdala neuronal FR to novel affectively relevant stimuli (fearful/disgusted faces and threat words, respectively) when presented subconsciously, as will be discussed below. Thus, selective amygdala neurons may be affected by conscious perception when preferred stimuli are familiar and biologically insignificant.

4. Affective processing

Contemporary neuroscience consistently implicates the human amygdala in emotion, or affective, processing (Phelps & Anderson, 1997; Vuilleumier, 2005). Here, we define emotion as an event-focused, two-step, rapid process consisting of (1)

relevance-based elicitation mechanisms that (2) shape a multi-componential response (i.e., action tendency, autonomic reaction, expression, and feeling) (Sander, 2013; p. 23). Critically, iEEG findings may offer particularly unique insight into amygdala neuronal processing of emotional stimuli. Moreover, these data may provide neurobiological evidence supporting contemporary emotion theories (see Sander (2013) for a discussion of how research on the amygdala can constrain theories of emotion). For instance, emotion-specific processing, such as fear, relates to processing of primary affective states reflecting basic emotion theories (e.g., Ekman, 1999). The potential role of the amygdala in the processing of valence (i.e., pleasantness or unpleasantness) and/or arousal underscores the bi-dimensional nature of emotions proposed by circumplex or core affect theories of emotion (e.g., Russell, 2003). Finally, affective relevance reflects the relevance detection component central to appraisal theories of emotion (Scherer, 1999). IEEG evidence may, therefore, be exceptionally useful in delineating amygdala neuronal functioning in response to affective processing.

4.1. *Face processing*

Intracranial research demonstrates human amygdala processing to be preferential to human faces, relative to neutral objects (Fried et al., 2002, 1997; Kreiman et al., 2000a; Pourtois, Spinelli, et al., 2010) and scrambled faces (Sato et al., 2011a, 2012), irrespective of conscious awareness (Willenbockel et al., 2012). A single-neuron study demonstrated a significant, albeit small, population of amygdala neurons to selectively process human faces, relative to categories and objects (Kreiman et al., 2000a) (Table 2). Two additional single-neuron studies illustrated that this preferential processing occurs at encoding and recognition (Fried et al., 2002, 1997), signaling a persistent face detection mechanism impervious to habituation effects from familiar stimuli. However, iLFP analyses have demonstrated an attenuation of amygdala amplitude subsequent to viewing a familiar face (Krolak-Salmon et al., 2004). It is important to consider that while Fried et al. (2002) observed consistent firing within the basolateral amygdala (BLA), Krolak-Salmon et al. (2004) observed potential habituation effects within the superficial nuclei of the amygdala. It is equally important to recognize potential averaging effects of two diametrically opposed neuronal populations within the superficial nuclei (Logothetis, 2003). Last, Krolak-Salmon et al. (2004) did not compare face processing against neutral object processing. These data thus demonstrate vigilance for familiar faces in the BLA yet potential habituation in the superficial nuclei.

The human amygdala has also been shown to respond differentially to isolated (Meletti et al., 2012; Sato et al., 2011a) and holistic (Rutishauser et al., 2011) features of human faces, regardless of emotional expression (Meletti et al., 2012; Sato et al., 2011a). When isolating eyes, two iLFP studies demonstrated increased amygdala amplitude and gamma oscillatory activity relative to isolated noses and mouths (Meletti et al., 2012) and scrambled faces (Sato et al., 2011a). Meletti et al. (2012) illustrated increased BLA amplitude to isolated eyes regardless of whether they expressed joy or fear. Moreover, Sato et al. (2011a) demonstrated that when compared to face mosaics, neutral eyes elicited significant amygdala gamma-band activity, regardless of gaze direction. Still, the basomedial amygdala nuclei may be sensitive to holistic features of human faces. Rutishauser et al. (2011) showed that when compared to isolated eyes and mouths, holistic features of whole faces evoked a significant percentage of basomedial amygdala neurons. These studies suggest that while particular regions of the human amygdala may be more vigilant toward social cues originating from the eyes, they may still reserve neurons to encode holistic features of the individual's entire face. Taken together, these studies demonstrate the amygdala to exhibit face-selectivity, irrespective of emotional expression that is primed by both eyes as well as holistic features and may occur at both conscious and subconscious levels.

4.2. *Fear processing*

While face processing may occur irrespective of emotional expression, extant iLFP literature suggests the human amygdala exhibits preferential treatment to affective stimuli expressing fear (Krolak-Salmon et al., 2004; Meletti et al., 2012; Pourtois, Spinelli, et al., 2010; Sato et al., 2011b) or signaling danger/threat (Naccache et al., 2005) as compared to neutral stimuli. Specifically, when observing emotional faces, attention to fearful, relative to neutral, faces elicits significantly greater human amygdala ERP (Krolak-Salmon et al., 2004; Meletti et al., 2012; Pourtois, Spinelli, et al., 2010) as well as theta-band (Meletti et al., 2012) and gamma-band (Sato et al., 2011b) activity. Furthermore, threatening stimuli elicit differential amygdala ERPs and oscillations occurring as early as 50 msec PSO (Table 3) (Krolak-Salmon et al., 2004; Meletti et al., 2012; Pourtois, Spinelli, et al., 2010; Sato et al., 2011b).

While this putative "fear effect" (Krolak-Salmon et al., 2004) witnessed in human amygdala neurons appears to distinguish between fearful/threatening and neutral stimuli, it remains uncertain whether it retains primacy over other aversive emotional expressions, particularly disgust. Krolak-Salmon et al. (2004) demonstrated that implicit processing of gender elicited late differential amygdala ERPs to fear and disgusted faces, relative to happy and neutral faces. This may thus result from an overall intensity or biological significance imbued in these aversive facial expressions. Moreover, only two single-neuron studies to date have compared amygdala neural response to fearful faces with response to happy, surprised, angry and neutral faces yet have shown results that conflict with the aforementioned iLFP data. For instance, Fried et al. (1997) demonstrated that single amygdala neurons spiked when presented with both female and male emotional faces but not to fear exclusively. Furthermore, Rutishauser et al. (2011) observed that amygdala neurons which distinguished whole faces from isolated facial features did not exhibit differential spiking activity to fearful faces. Consequently, social cognitive affective neuroscience would benefit from further exploration of amygdala neuronal responding to fearful versus non-fearful faces, perhaps by manipulating eye-gaze direction thereby changing the origin of perceived threat and thus increasing the face's self-relevance value (cf. Cristinzio, N'Diaye, Seeck, Vuilleumier, & Sander, 2010; Wicker, Perrett, Baron-Cohen, & Decety, 2003). Therefore, while iLFP studies

evidence differential amygdala neuronal response to fearful faces and threat-inducing stimuli, two single-neuron studies illustrate potentially valence-general face processing within the human amygdala. Given that the intensity of the emotional expression may play an elemental role in the variance of human amygdala neuronal processing of faces, it would be essential to evaluate the degrees of arousal elicited by these stimuli.

4.3. *Arousal processing*

Arousal may be a crucial factor underlying amygdala neural response to affective stimuli, yet it remains a seldom investigated variable in iEEG studies. Arousal represents the psychophysiological state of elevated vigilance and reactivity to one's environment, induced by endogenous and/or exogenous stimuli, and typically associated with increased activity in the sympathetic nervous system. Aversive stimuli may inherently possess features which render them more emotionally arousing than pleasant or neutral stimuli (c.f. Canli et al., 2000; Krolak-Salmon et al., 2004; Oya, Kawasaki, Howard, & Adolphs, 2002). A correlation between negative valence and arousal has been reliably demonstrated whereby increasing stimulus negativity relates to increasing subjective arousal (Canli et al., 2000). Corroborating these findings, an iEEG study demonstrated a relation between aversive stimuli, subjective arousal, and amygdala oscillatory activity whereby both highly arousing and aversive stimuli drove amygdala gamma-band power responses (Oya et al., 2002). Consequently, this begs the question of their independence. For this reason, we infer amygdala sensitivity to affectively averse stimuli attributes which equally induce elevated vigilance and arousal. These suspicions notwithstanding, evidence from a single-neuron study suggests the amygdala may prefer biologically significant to arousing stimuli (Mormann et al., 2011). Mormann et al. (2011) demonstrated differential amygdala firing to animal, relative to non-animal, images matched for subjective valence and arousal levels. The amygdala may thus share dual mechanisms, processing arousing/aversive stimuli but also biologically significant stimuli independently of arousal processing.

Aversive emotional events take the form not only of threat but of goal-obstruction whereby achieving one's goal is impeded (Brázdil et al., 2002; Pourtois, Vocat, et al., 2010). Pourtois, Vocat, et al. (2010) argued such aversive anomalies are "rare, negative and interfering events, which need to be avoided, and can even activate the defensive/aversive motivational system" (p. 1155). This can be empirically operationalized as performance errors and procedural impediments which obstruct one's fluid performance and, by extension, one's overall goal of accomplishing the respective task. Additionally, anomalous events (e.g., no-go stimuli, procedural glitches) may be relatively arousing as they punctuate what would otherwise be a continuous stream of 'go' events to which the participant may habituate psychophysiologically. These types of events were implemented in two iLFP studies (Brázdil et al., 2002; Pourtois, Vocat, et al., 2010). Although neither subjective nor objective measures of arousal were administered, these two studies suggest errors and false alarms to be experienced as aversive and possibly arousing in the context of task-relevant paradigms (Brázdil et al., 2002; Pourtois, Vocat, et al., 2010). Pourtois, Vocat, et al., 2010 observed early response-locked amygdala ERPs to active responses only (i.e., errors, fast hits, slow hits) ~25–320 msec PSO in a go/nogo task (Table 3). Brázdil et al. (2002) equally found early response-locked amygdala ERP potential in reaction to active error responding ~122–350 msec PSO. Future research may wish to consider, therefore, that performance errors and procedural obstructions bear a degree of arousal, as they tend to be viewed as unexpected, rare, and aversive events related to one's motivational self-relevant goals.

4.4. *Relevance*

Stimuli bearing some relation with one's motivational goals would engender a degree of relevance. Relevance, or significance (cf. Padmala, Lim, & Pessoa, 2010; Pessoa & Adolphs, 2010), reflects phenomena affecting the maintenance and integrity of the self (Markowitsch & Staniloiu, 2011), which is constituted by goal-acquisition, coherence and cohesion of the conceptual and working self (e.g., value preference and judgment) (Jobson, 2009), basic needs satisfaction, and overall survival (Conway & Pleydell-Pearce, 2000). For instance, relevance may lie in the degree of behavioral or motivational relevance attributed to any given agentic behavior or stimulus, respectively that facilitates the achievement of a personal goal. Importantly, habituation effects discussed above may be due specifically to relevance detection whereby familiar information is filtered for relevance and consolidated while novel information is still treated as potentially relevant until adequate processing confirms or rejects its significance to the individual (Pedreira et al., 2010). In a single-neuron study, Pedreira et al. (2010) witnessed high amygdala selectivity to novel events. Critically, this selectivity was not linked with the novelty of the event, per se, but to specific stimuli (Pedreira et al., 2010), thus intimating a primacy of intrinsic value (e.g., self-relevance) over novelty alone. While complementary functions such as novelty/familiarity detection, arousal processing and memory should not be discounted, this study suggests that specific amygdala neurons may scan the environment for relevance amongst novel stimuli (Pedreira et al., 2010).

While contemporary neuroscience literature supports amygdala relevance processing (Pessoa & Adolphs, 2010; Sander et al., 2003), intracranial data evidence a direct relation between amygdala neuronal activity and relevance processing, both implicitly (Brázdil et al., 2002; Viskontas, Quiroga, & Fried, 2009) and explicitly (Jenison, Rangel, Oya, Kawasaki, & Howard, 2011). Concretely, these iEEG data have delineated two broad types of amygdala relevance processing: (i) behavioral and (ii) motivational.

4.5. *Behavioral relevance*

Behavioral relevance attributes significance to one's own behavior or a task in which one feels his/her self to be implicated. Specifically, the degree to which one's motor planning and actions promote goal-acquisition, self-affirmation, basic needs satisfaction, and overall survival would be considered as bearing a degree of behavioral relevance to

one's self. Unlike motivational relevance, therefore, behavioral relevance applies principally to one's own agentic movements, behavior, and actions. Motor planning and action can be evaluated empirically via error performance monitoring and detection, often operationalized as a go/nogo task (Kohls et al., 2013). Notably, iLFP studies demonstrate significant increases in amygdala ERP amplitude subsequent to performance errors. Brázdil et al. (2002) observed differential amygdala potentials to go/nogo performance errors ~122 msec and ~350 msec PSO (Table 3) and attributed the latter effect to a late positivity component considered to be involved in error detection (Brázdil et al., 2002; Leuthold & Sommer, 1999). This may thus be indicative of processes responding to active error responses and their resulting goal-obstruction. Additionally, Pourtois, Vocat, et al. (2010) witnessed amygdala sensitivity to go/nogo performance monitoring, observing significantly delayed ERP amygdala modulations during commission errors. Notably, ERP modulations occurred only around the patients' active response, as they witnessed no ERP modulations during passive rejection of a stimulus. This may equally imply direct involvement in active, and possibly agentic, performance monitoring (Pourtois, Vocat, et al., 2010). Moreover, these ERP modulations appeared tens of milliseconds before a correct response and roughly 300 msec subsequent to a commission error. This evidence suggests the amygdala produces differential responding to behavioral performance, with earlier neural activity to correct than erroneous responses.

A single-neuron study supports amygdala neuronal responding to agentic behavioral relevance detection (Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010), demonstrating dissociated neuronal firing to agentic action execution and observation of third-party action execution (Table 2). This action execution-observation dissociation suggests the presence of amygdala neurons dedicated to self-agency via activation/inhibition during execution/observation (Mukamel et al., 2010), which further underscores a role of amygdala in behavioral relevance.

4.6. *Motivational relevance*

The iEEG literature also implicates amygdala neurons in the processing of motivational relevance. Here, we discuss motivational relevance in terms of learned value or significance for one's biological needs, both of which are subjectively fitted to the specific concerns of the individual. Unlike behavioral relevance, this may relate to stimuli/events affecting self-promoting pursuits like goal-acquisition, self-affirmation, basic needs satisfaction, and overall survival. Two single-neuron studies have demonstrated amygdala involvement in processing motivational relevance (Jenison et al., 2011; Viskontas et al., 2009). Using a judgment preference task, Jenison et al. (2011) illustrated the amygdala to be involved in either encoding or computing of the value of the respective stimulus during the time of choice (Jenison et al., 2011). Specifically, authors observed nearly a third of recorded amygdala neurons firing linearly with one's preferred choice bid (Table 2), suggesting amygdala involvement in valuation, particularly stimulus value computations at time of choice (Jenison et al., 2011). This study indicates a linear relation between amygdala neuronal firing and motivational relevance processing in external stimuli.

Motivational relevance processing was equally implied when identifying the faces of proxy caregivers. In a single-neuron study, patients identified individual faces differing in levels of familiarity and relevance (Viskontas et al., 2009). Stimuli included faces of self, family members, the experimenters, famous politicians and celebrities, and complete strangers as well as non-face control images such as landmarks. Although the amygdala yielded selective excitatory neuronal firing to faces, activity proved greater for experimenters than for all other face categories. Interestingly, family and self were statistically equal to faces of celebrities and strangers. Authors concluded that the amygdala may be involved in processes related to salience/novelty and emotional significance (Viskontas et al., 2009). Together, these single-neuron studies implicate amygdala neurons in relevance processing in both valuation of preferred objects and in viewing faces of potentially self-relevant others (cf. Murray, Schaer, & Debbane, 2012).

5. Latency components

Intracranial literature demonstrates both amygdala potential and oscillatory activity to respond to novel and affective external stimuli in three time latency windows, consisting of early (~50–290 msec), intermediate (~270–470 msec), and late (~600–1400 msec) effects PSO. The amygdala exhibits early effects from human face and emotional expression processing (Krolak-Salmon et al., 2004; Pourtois, Spinelli, et al., 2010; Sato et al., 2011b, 2012; Willenbockel et al., 2012), intermediate effects to rare events (Halgren et al., 1980; Jung et al., 2006; Stapleton & Halgren, 1987), and late effects to tasks demanding high cognitive load (Dellacherie et al., 2009), attention (Krolak-Salmon et al., 2004; Pourtois, Spinelli, et al., 2010), or semantic processing (Naccache et al., 2005). Below, we highlight the findings from iLFP studies investigating human amygdala response times to experiencing novel and affective stimuli. Consequently, this section excludes a discussion on iLFP studies which either required patients to conduct an explicit behavioral task, (e.g., go/nogo) (e.g., Brázdil et al., 2002; Pourtois, Vocat, et al., 2010) or altered/filtered their stimuli for biased attention toward specific salient features (e.g., eyes) (e.g., Meletti et al., 2012; Sato et al., 2011a).

5.1. *Early effects*

Evidence suggests the implicit priming of novel and affectively relevant stimulus features creates effects on amygdala potential ~50–290 msec PSO (Pourtois, Vocat, et al., 2010; Sato et al., 2011b, 2012; Willenbockel et al., 2012). A time-frequency analyses demonstrated differential high-gamma-band amygdala activity to fearful, relative to neutral, faces at ~50 msec when patients attended to gender (Table 3) (Sato et al., 2011b). At a later latency, amygdala neurons demonstrated differential gamma-band activity ~200–300 msec to neutral faces, relative to houses (Sato et al., 2012). Still,

Pourtois, Spinelli, et al. (2010) illustrated differential amygdala amplitude to fearful, relative to neutral, faces ~140–290 msec irrespective of whether or not attention was directed toward the faces (Table 3). Additionally, Willenbockel et al. (2012) observed differential amygdala activity to fearful and disgusted faces at both subconscious (~140 msec) and conscious (~240 msec) levels. These results suggest an early exogenous (i.e., stimulus-driven) modulating effect of affective or motivationally relevant stimuli on amygdala potential whilst either implicitly attending (e.g., attending to gender) to affective stimuli or when receiving subconscious biologically significant percepts from the environment.

Intracranial evidence equally suggests early exogenous modulating effects on amygdala neural activity in response to explicit attention to an affectively laden task-relevant stimulus. Explicit attention refers to volitional enhancement of affective or task-relevant features of the target stimulus, like judging the emotional expression of a face (e.g., Halgren et al., 1994; Krolak-Salmon et al., 2004) or counting the number of rare events in an oddball task (e.g., Halgren et al., 1980; Stapleton & Halgren, 1987). Notably, iEEG literature illustrates the emergence of the same neural pattern of early amygdala potential, independent of sensory modality, ~50–250 msec when explicitly attending to affective features of a target stimulus (Halgren et al., 1994; Krolak-Salmon et al., 2004; Oya et al., 2002). Krolak-Salmon et al. (2004) illustrated that attending to the emotional expression of a face induces significantly greater amygdala ERP amplitude to fearful than disgusted, happy and neutral faces, emerging at ~200 msec. Similarly, Halgren et al. (1994) found explicit attention to emotional expressions elicits greater amygdala ERP potential to novel, versus, familiar faces at ~287 msec. Finally, passive viewing of affective images evoked early low gamma-band amygdala activity ~50–250 msec PSO and high-gamma-band activity at ~150–250 msec (Oya et al., 2002) to unpleasant, relative to pleasant, stimuli. Taken together, these findings signal early effects of affective processing on human amygdala neurons ~50–290 msec PSO.

5.2. *Intermediate effects*

Intracranial data illustrate novel and infrequent auditory/visual events to principally evoke amygdala ERP within the intermediate latency window of ~270–470 msec PSO. This has been demonstrated via iLFP (Halgren et al., 1994, 1980; Stapleton & Halgren, 1987) and time-frequency (Oya et al., 2002) analyses. Specifically, attending to the number of rare auditory tones and visual symbols has elicited significant amygdala ERPs at ~265–430 msec (Halgren et al., 1980). Importantly, rare/frequent stimuli were both neutrally valenced and were comparable in intensity and spatial-frequencies (Halgren et al., 1980). When using affective stimuli such as faces, however, Halgren et al. (1994) witnessed additional preferential amygdala potential amplitude ~468 msec to novel, relative to familiar, faces when patients explicitly attended to valence and intensity of the face's emotion expression, signaling an intermediate primacy of novelty over affective salience. Additionally, Stapleton and Halgren (1987) demonstrated significantly greater amygdala ERP ~300–400 msec for rare versus frequent auditory stimuli (Table 1, Table 3). Critically, this effect was present only when patients counted the number of rare tones. When ignoring such tones (i.e., reading a book), amygdala ERPs were attenuated (Halgren et al., 1980; Stapleton & Halgren, 1987). These findings suggest novelty processing, independent of sensory modality yet modulated by attention allocation. Next, Jung et al. (2006) observed increased amygdala ERP amplitudes to novel, relative to familiar, odors ~349 msec. Authors additionally showed stronger gamma oscillations in response to novel, relative to familiar, odors (Table 3). Finally, Oya et al. (2002) found amygdala high-gamma-band activity in response to affectively laden images at ~350–450 msec, increasing for unpleasant, relative to pleasant, stimuli. Thus, explicit attention to novel and affectively laden stimuli may relate to differential amygdala ERP and oscillatory activity within the intermediate window of ~270–470 msec PSO.

5.3. *Late effects*

During the late latency window of ~600–1400 msec PSO, amygdala neurons exhibit a reliance on complementary cognitive functions such as attention (Dellacherie et al., 2009; Halgren et al., 1994; Krolak-Salmon et al., 2004) and semantic processing (Naccache et al., 2005). Halgren et al. (1994) witnessed differential amygdala amplitude ~665 msec to familiar, relative to novel, faces and words when patients attended explicitly to the valence and intensity of emotional expressions (Table 3). Additionally, when comparing the likeness between two faces, Pourtois, Spinelli, et al. (2010) observed slow wave amygdala ERP occurring ~710 msec in response to both fearful and neutral faces relative to averting attention away from the target stimuli. Similarly, Krolak-Salmon et al. (2004) demonstrated that implicit attention to gender yielded differential slow wave amygdala potential at ~600–800 msec, but only to fearful and disgusted faces, relative to happy and neutral faces. The fear effect witnessed during earlier stages thus seems to disappear within the slow wave component when implicitly attending to emotional faces. However, emotional arousal or motivational relevance may still underlie the differences between more aversive and more pleasant stimuli given that both disgust and fear elicited significant amygdala ERPs (Krolak-Salmon et al., 2004; Oya et al., 2002). Semantic processing of threat concepts, albeit subconsciously, also elicits late amygdala potential. Naccache et al. (2005) observed the amygdala to differentially respond to masked threat words ~870 msec, suggesting a late processing of semantic and affectively laden information, even at subconscious levels. While this seemingly conflicts with Kreiman et al. (2002), Naccache et al. (2005) presented threat stimuli at initial encoding, thus arguably evoking processes related to motivational relevance and novelty detection. Finally, Dellacherie et al. (2009) observed differential amygdala potential ~1200–1400 msec when patients counted dissonant, relative to consonant, chords. Authors suggested the influence of emotional processing (Dellacherie et al., 2009), yet extant EEG literature may better support an explanation of top-down executive processes regulating an increasing cognitive load of retained information (Diamantopoulou, Poom, Klaver, & Talsma, 2011; Klaver, Talsma, Wijers, Heinze, & Mulder, 1999). Taken together, these data suggest deferred amygdala

processing of affective stimuli which may be accompanied by complementary cognitive functions related to attention, semantic processing, and working memory.

6. Discussion

Over the past four decades, nearly 50 single-neuron, iLFP and time-frequency analyses have provided insight into the spatially and temporally precise neuronal responses of the human amygdala in light of cognitive-behavioral task-dependent processing (see Table 1). In so doing, this collection of empirical data has contributed uniquely to our understanding of human amygdala functioning.

Our iEEG review contributes to the current discussion on mechanisms underlying amygdala neuronal functioning, particularly its role in affective processing, in five ways. First, we delineate timing of effects on amygdala functioning into three latency windows. The early window (~50–290 msec PSO) comprises effects from stimulus-driven face and affective processing. The intermediate window (~270–470 msec PSO) includes effects from novelty detection of task-relevant stimuli. The late window (~600–1400 msec PSO) comprises effects from semantic processing, familiarity detection, and attentional focus. Second, we outline consistent iEEG evidence in favor of an object-based/category-based selective encoding/detection mechanism in the human amygdala, irrespective of sensory modality and visual-spatial context. Third, our review underscores amygdala neuronal selectivity to faces as well as biologically significant stimuli like animals and relevant others. Fourth, we highlight the existence of dissociable human amygdala neuronal populations dedicated to familiarity and novelty detection of potentially relevant stimuli. Finally, we underline the direct relation between amygdala neuronal activity and affective relevance. We will now discuss each of the topics in greater detail, following the sequence in the main body of the review.

6.1. *Memory formation*

Context-independent selective encoding/detection, as highlighted in this review, would suggest amygdala neuronal reliance on semantic associations during encoding and recognition and appears to relate to both a sensitivity toward novel relevant stimuli and a habituation to familiar affective stimuli. Importantly, amygdala contextual recall decays after 24 h while familiarity-novelty distinction remains nevertheless intact (Rutishauser et al., 2008). Furthermore, iEEG data suggest amygdala storage of object-based/category-based information relies not upon context but semantic meaning, arguably in relation to its imbued biological significance. Together, our review delineates human amygdala neuronal selective encoding/detection, irrespective of context, with response sensitivity to novel task-relevant stimuli and habituation to familiar affectively laden stimuli.

6.2. *Affective processing*

In this review, we conducted an exhaustive exploration of the affective components underlying amygdala neuronal functioning within the iEEG literature. Although an important iEEG review of human MTL iEEG studies has recently been conducted (Suthana & Fried, 2012), the analysis of the collected iEEG studies was targeted toward neither amygdala functioning, per se, nor the affective components underlying amygdala neuronal functioning. Given the amygdala's evidenced role in emotion processing (Phelps & Anderson, 1997; Vuilleumier, 2005) we aimed to deconstruct the relation between amygdala functioning and emotion processing. Our review delineates amygdala face-processing selectivity, particularly when expressing aversive emotions like fear and disgust, that may manifest irrespective of conscious awareness (Willenbockel et al., 2012). These findings appear to conflict with Kreiman et al. (2002) who showed no amygdala response to masked target objects. Importantly, these two studies analyzed neuronal firing at two different periods: encoding (Willenbockel et al., 2012) and recognition (Kreiman et al., 2002). Thus, it is possible that the amygdala response reported in the former study may be related to novelty processing. Critically, while Kreiman et al. (2002) used objects, Willenbockel et al. (2012) presented human faces which may carry significantly greater biological significance.

IEEG data conflict on the specificity of amygdala processing of eyes, however. Whereas the basolateral nuclei demonstrate eye-specific processing, the basomedial nuclei appear to prefer holistic facial features. Still, lesion data support the amygdala's role in capturing social cues from eyes, arguably for the evolutionary processes of discriminating emotion expressions (Adolphs et al., 2005). Unfortunately for the majority of reviewed iEEG studies, it remains uncertain whether amygdala neuronal activity specifically reflects incoming affective information (e.g., fear) (Hietanen & Astikainen, 2013), arousal (Hietanen & Nummenmaa, 2011), or face-processing artifacts from shared networks (Rellecke, Sommer, & Schacht, 2013). These processes have been demonstrated to elicit ERP amplitude ~170–220 msec (Navajas, Ahmadi, & Quian Quiroga, 2013; Nguyen & Cunnington, 2014; Rellecke et al., 2013; Schupp et al., 2004; Streit et al., 1999), which overlap with early iEEG latency window outlined in this review. Future iEEG studies controlling for each individual process (affective processing, arousal, face-processing) are thus warranted.

In fact, a plausible explanation for fear discrimination illustrated in iEEG data may be due to arousal rather than threat processing, per se. That is, eye-gaze direction of fearful faces may play a key role in arousal and threat processing, as is suggested by neuroimaging evidence in healthy (Wicker et al., 2003) and lesioned (Cristinzio et al., 2010) participants. While Sato et al. (2011a) showed that both direct and averted gaze elicited differential amygdala neuronal activity, they did not control for emotion. Future iEEG investigation controlling for averted gaze and emotional expression is necessary to distinguish arousal, emotion, and self-relevance processing. Furthermore, future iEEG studies may wish to employ an emotional face inversion task to delineate face from emotion processing (cf. Rellecke et al., 2013). Upon review of iEEG data, it remains equally indiscernible whether amygdala sensitivity to affective stimuli persists in light of averted allocation of attentional resources (cf. Pessoa, McKenna, Gutierrez, & Ungerleider, 2002). Future research would thus benefit from

manipulating cognitive load when averting attention away from affective stimuli. Additional research on the role of the amygdala in multimodal emotional attention (see Brosch, Grandjean, Sander, & Scherer, 2008) would also be important.

Self-relevance may equally be an underlying factor in amygdala processing of affective cues. The amygdala has been presumed to play a pivotal role in the detection and encoding of relevance in one's external environment as a functions of one's goals, needs, values and well-being (Cunningham & Brosch, 2012; Sander et al., 2003). Anomalous procedural events, such as false alarms (cf. Brázdil et al., 2005; Pourtois, Vocat, et al., 2010), invoke a degree of behavioral relevance as they impede goal-achievement. Important differences exist between two reviewed iLFP studies examining behavioral relevance. Pourtois, Vocat, et al. (2010) observed significant amygdala ERP subsequent only to active key-presses, independent of accuracy. When false alarms were correctly rejected (i.e., no active response), the amygdala exhibited no significant ERPs. Notably, however, false alarms were not infrequent. Whereas Brázdil et al. (2002) induced roughly 9 errors per patient, Pourtois, Vocat, et al. (2010) induced between 30 and 40 errors, thus significantly reducing the novelty of false alarms, as duly noted by the authors (Pourtois, Vocat, et al., 2010). These two iEEG studies revealed the human amygdala to be involved in performance monitoring and error detection, however future research is nevertheless warranted to disentangle amygdala ERP activity and its motivational and novelty-detection properties. Coupled with induced procedural anomalies, such as technical errors, one could begin to discern arousal and novelty from motivationally-defensive responses to performed errors (Hajcak & Foti, 2008; Pourtois, Vocat, et al., 2010). Notably, iEEG data demonstrate dedicated human amygdala neurons to self-agentic behaviors, thus underscoring the amygdala's role in task-relevant processing. Taken together, iEEG evidence suggests the human amygdala to process self-agentic behavior execution, particularly that which directly pertains to task-relevant goals.

Single-neurons studies also present evidence indicating appraisal of motivational relevance. First, Jenison et al. (2011) illustrated amygdala neuronal FR to coincide with valuation of preferred bids. Still, these authors conceded that the arousal and attentional responses that appetitive stimuli generate are likely to correlate with their attributed value. Therefore, it is possible that amygdala neuronal firing subsumes emotional arousal and attentional responding elicited by appetitive stimuli. To our knowledge, this iEEG study represents the first to directly examine the relation between subjective valuing and appraisal of motivational relevance of external stimuli and neuronal activity within the amygdala. More research replicating and elaborating upon the present study would be warranted in order to develop reliable conclusions on the amygdala's direct involvement in valuing of external stimuli. Next, Viskontas et al. (2009) illustrated differential amygdala FR to faces of people differing in degrees of personal relevance. In their single-neuron study, the authors demonstrated that images of experimenters elicited greater amygdala FR than family and self. While family members and self both possess affective relevance (Murray et al., 2012), experimenters may indeed bear a level of self-relevance as well, as they serve as the proxy caretakers of these patients during their perioperative period. Novelty detection, however, does appear to be quite prominent nonetheless, as we see equal neuronal firing in the amygdala in response to strangers as to celebrities, family and self. Future research measuring subjective levels of affective or self-relevance that these individuals carry for each patient, in addition to psychophysiological measures analyzing arousal levels, would be important to control for arousal as well as to correlate amygdala neuronal firing with subjective levels of relevance.

6.3. *Latency components*

The iEEG literature reviewed above equally provides insight into the timing of effects (PSO) on amygdala neuronal functioning. Specifically, we highlighted early effects manifesting as differential high-gamma-band activity in response to affective information like faces relative to houses (200–300 msec), fearful relative to neutral faces (50 msec) and unpleasant relative to pleasant images (150–250 msec) (Oya et al., 2002). Effects also occurred when attending to gender of fearful versus neutral faces (150 msec) and emotional expression of fearful versus neutral faces (200 msec). In human MEG studies, early amygdala event-related gamma-band (20–30 msec) is shown to discriminate fearful from angry and neutral faces (Luo, Holroyd, Jones, Hendler, & Blair, 2007), while differential amygdala gamma-band relates to emotion discrimination in humans (Luo et al., 2009). The reviewed early effects of emotion on amygdala iLFP amplitude accord with extant EEG/MEG data, which illustrate neural activity specific to face-processing at ~170 msec (Navajas et al., 2013; Nguyen & Cunnington, 2014; Rellecke et al., 2013) and to emotional face-processing at ~200–220 msec PSO (Schupp et al., 2004; Streit et al., 1999). Early amygdala processing implies an automatic and direct neural pathway rapidly processing biologically significant information. This would suggest amygdala communication with subcortical pathways (Dolan & Vuilleumier, 2003; Ohman, Carlsson, Lundqvist, & Ingvar, 2007), such as the thalamus as previously exhibited in rodents (LeDoux, 2003, 2000), which may speak to automatic "low-road" treatment of environmental stimuli (LeDoux, 1994, 2000). Critically however, human amygdala neuronal activation occurs later ($\geq$50 msec PSO) than rodent activation ($\leq$20 msec PSO) to threat-inducing stimuli (Repa et al., 2001). Future analyses would thus benefit from concomitant recordings in these respective subcortical structures (e.g., thalamus). Together, reviewed iEEG findings signal early automatic exogenous emotion-driven encoding mechanisms, sensitive to faces and emotional expressions bearing a degree of arousal and biological significance.

Endogenous effects of volitional cognitive control toward task-relevant targets, however, are implicated in the intermediate window of ~270–470 msec PSO, during which time iEEG data illustrate the amygdala to respond to novel target events, irrespective of sensory modality. EEG literature has associated this window with stimulus- and response-related processing (Brázdil, Roman, Daniel, & Rektor, 2003) wherein cortical potential emerges in response to rare task-relevant events (Brázdil et al., 2005; Patel & Azzam, 2005). Neural

activity within this latency window may recruit a distributed network of cortical/subcortical areas (Halgren, Marinkovic, & Chauvel, 1998) composed of anterior and posterior (Polich, 2007) regions and may subsume endogenous processes related to attention and working memory (Polich, 2003). Our review thus highlights intermediate effects related principally to detection of novel task-relevant stimuli.

Finally, this review distilled late effects on amygdala neurons. Studies primarily targeted attention and semantic processing. Amygdala neurons responded to implicit (710 msec) and explicit (600–800 msec) attention toward emotional faces, however, the discrimination between fearful and non-fearful faces is attenuated in both conditions. Additionally, the amygdala appears to respond equally to the biological significance imbued in the affective cues of disgust and fear (Krolak-Salmon et al., 2004), although any conclusion thereupon is premature without further investigation into the nature to which the patient finds the stimuli arousing and/or self-relevant. Additionally, memory retrieval and semantic associations may contribute to effects within slow wave amygdala potential witnessed at ~665 msec when differentiating familiar from novel faces (Halgren et al., 1994; Riby & Orme, 2013). Next, subconsciously perceiving threatening words, relative to non-threatening words, elicited increased late amygdala ERP amplitude (870 msec), suggesting an implicit but deferred recruitment of semantic memory from subliminal environmental percepts. Finally, counting dissonant chords, relative to consonant chords, elicited differential amygdala amplitude (1200–1400 msec), which the authors attribute to emotion processing. Still, effects within this late window have been linked to working memory, encoding and memorization (Diamantopoulou et al., 2011), particularly when cognitive load is high (Klaver et al., 1999). Given the nature of the task, we consider the plausible influence of working memory facilitating novel dissonant stimuli encoding and frequency memorization (cf. Diamantopoulou et al., 2011). Taken together, the late effects on amygdala neuronal activity appear to comprise a recruitment of executive processes related to semantic retrieval, working memory, and memorization of task-relevant stimuli.

6.4. *Clinical significance*

Our reviewed data highlight several potential areas of significance to clinical research. First, contextually-independent selective encoding/recognition may relate to flashback memories often observed among individuals suffering from post-traumatic stress disorder (PTSD). Flashback memories consist of sudden involuntary, yet vivid, remembrances of specific memories during a traumatic event that are devoid of context. Frequently associated with amygdala hyperactivity (Koenigs et al., 2008), flashback memories may relate to selective semantically primed memories, dissociated from contextual encoding (cf. Newport & Nemeroff, 2000; Skelton, Ressler, Norrholm, Jovanovic, & Bradley-Davino, 2012), as illustrated by iEEG data.

Second, while iEEG data reviewed above present little evidence of long-term contextual encoding, it is plausible that the stimuli in the reviewed studies remained below a level of biological significance strong enough to induce synaptic long-term potentiation needed to induce contextual conditioning (Sah, Westbrook, & Luthi, 2008). Ample evidence illustrates the amygdala's role in contextual learning under fear conditioning scenarios (Fanselow & LeDoux, 1999; Sah et al., 2008) in rodents (Chau, Prakapenka, Fleming, Davis, & Galvez, 2013; Flavell & Lee, 2012; Trogrlic, Wilson, Newman, & Murphy, 2011) and in human neuroimaging (Hughes & Shin, 2011) and lesion (Koenigs et al., 2008) studies. As none of the iEEG studies reviewed used a conditioning task, future iEEG research would benefit from employing context learning paradigms controlling for arousal, self-relevance, and threat in order to assess the full nature of selective encoding and potential contextual encoding in human amygdala neurons relative to fear and anxiety-related behaviors in healthy and clinical populations (Brocke et al., 2010).

Finally, amygdala familiarity detection highlighted above may relate to a key impairment in borderline personality disorder (BPD), a psychological condition marked by extreme affective instability. Recent neuroimaging data delineated an important relation between deficient behavioral habituation to emotional stimuli and abnormal amygdala-insula functional connectivity amongst BPD individuals (Koenigsberg et al., 2014). As reduced amygdala functioning and volume is consistently reported to contribute to BPD symptomatology (Hazlett et al., 2012; Ruocco, Amirthavasagam, & Zakzanis, 2012), future iEEG research delineating novelty and familiarity detection amongst affectively relevant stimuli would be instrumental to better understand amygdala's role in such processing in healthy and BPD individuals.

7. Conclusion

This review of 47 iEEG studies investigating amygdala neuronal functioning has highlighted processes related to memory formation and affective processing. We equally delineated three time latency windows consistent of early, intermediate and late effects on amygdala neuronal activity. Within memory formation, we witnessed reliable evidence in favor of a selective encoding/detection mechanism, irrespective of context, sensory modality, and presentation condition. We observed evidence indicative of novelty detection and familiarity habituation, particularly when perceiving affective stimuli. Nonetheless, familiarity recognition may rely on a reciprocal relation between conscious perception and amygdala neuronal firing in face of the preferred object. Within affective processing, our review evidences reliable face-processing selectivity underlying amygdala neuronal functioning wherein aversive emotional expressions and information from eyes may retain primacy. Additionally, our review illustrates human amygdala neurons to respond differentially to task-relevant performance errors as well as self-relevant behavioral bids to preferred choice objects. Finally, our review delineates timing of effects in amygdala neuronal activity to occur in three latency windows: early, intermediate, and late. The early window subsumes effects respective to exogenous stimulus-driven affective processing of faces and emotion. This may include implicit and explicit attention to the target stimulus, however, it is still unclear how endogenous factors, such as attentional load, may play a

role in exogenous influences of external stimuli. The intermediate window comprises effects related to explicit attention to novel task-relevant stimuli, irrespective of sensory modality. The late window subsumes effects from tasks soliciting working memory, semantic processing, attentional focus and memorization during affective processing. These data hold clinical significance for psychological conditions related to PTSD, anxiety-related behavior, and BPD. Future investigations testing for degrees of arousal and self-relevance are nonetheless warranted.

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