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Perception of negative affect in schizophrenia – functional and structural amygdala changes. Review

Modern neuroscience has provided us with a foundation for understanding schizophrenia in terms of brain dysfunction. Imaging techniques revealed graphically the linkage between patterns of brain activity and patterns of mental activity enabling to explore neural correlates of "emotional brain" in normals and schizophrenic patients. Obviously, schizophrenia is an illness that can be difficult to explain or define because patients have so many different kinds of symptoms. The most striking thing about schizophrenia is its sweepingly broad injury to a large array of cognitive and emotional systems in human brain (2).

Bleuler (1911) defined schizophrenia as essentially a splitting of thoughts (cognition) from feelings (emotion). "Flattening of affect" has been recognised as a core feature of schizophrenia since its first description. Furthermore, schizophrenia has been found to be strongly related with disordered appraisal and experience of negative affect, such as threat or anger. From an evolutionary perspective, fear is one of the most important expressions to recognize quickly. Rapid detection of this emotion has implications for survival – an individual unable to detect fear on the face of a conspecific may be exposed to a dangerous or life-threatening situation. It is also necessary to know whether the fearful expression seen is emerging or dissipating, the former having implications for survival, while the latter implies that the danger may have passed.

Amygdala is a structure which acts as an "emotional manager" in rapid, coarse, perceptual processing of highly arousing emotions particularly fear, though in human lesion studies evidence was found for a wider impairment in processing multiple emotions of negative valence, including additionally anger, disgust, and sadness (1). The amygdala is a bilateral, ovoid, grey matter structure, on the super medial surface of the temporal lobe, anterior to and partially overlapping with the hippocampal formation. The major input region of the amygdala is the lateral nucleus, which receives convergent afferents from all sensory modalities. Furthermore, it is richly connected to thalamic nuclei, hippocampus and temporal and posterior orbitofrontal cortices and this connectivity reflects its principal function: to evaluate the emotional salience of sensory input, and to store and to retrieve information of emotional significance to guide behaviour (9). Functional and structural abnormalities of the amygdala have been repeatedly explored utilizing morphological procedures and functional imaging.

FUNCTIONAL AMYGDALA CHANGES TO NEGATIVE EMOTIONAL STIMULI IN PATIENTS WITH SCHIZOPHRENIA

Despite the evidence for impaired perception of negative affect in schizophrenia, there have been a few functional neuroimaging studies so far examining neural responses to facial negative emotional stimuli in this illness (Tab. 1). Fearful faces in particular have consistently activated the amygdala. Such activity may be relatively "automatic", as it can arise without any requirement for explicit judgment of facial expression (e.g., as when subjects make gender judgments (8). PET facilitates the evaluation of cerebral metabolic activity and regional cerebral blood flow in resting brain, or to map cerebral activation during emotional or cognitive tasks (12).

Table 1. Functional amygdala changes in schizophrenia: review of recent functional magnetic resonanse imaging

fMRI study	Key findings
Schneider et al. 1998	No amygdala activation in schizophrenic patients during sad and happy mood induction
Phillips et al. 1999	No amygdala activation during gender discrimination of facial emotional expressions in schizophrenic patients
Kosaka et al. 2002	Increased amygdala activation in schizophrenic patients and controls during positive and negative emotion discrimination task
Gur et al. 2002	Failure to activate limbic regions during emotional valence discrimination may explain emotion processing deficits in patients with schizophrenia

Taylor et al. (2002) compared limbic-emotional function of schizophrenic patients with that of healthy controls during (^{15}O)water positron emission tomography (PET) using aversive and non-aversive pictures. The results revealed greater activation of the medial prefrontal cortex for the aversive stimuli in schizophrenic patients, whereas they had significantly less activation in the left mid occipital gyrus and left fusiform gyrus. Interestingly, activity in the left amygdala correlated with positive symptoms in schizophrenic subjects (15).

Functional MRI (fMRI) with its spatial resolution of 1 mm, and temporal resolution of around one second allows for very precise mapping of cognitive functions, helping to identify structures and functional networks that may be abnormal in schizophrenia (12).

Studies have demonstrated that schizophrenic patients relative to healthy controls fail to activate the amygdala in response to facial expressions of fear (8), and also during a sadness induction paradigm (11). Compared with non-paranoid schizophrenic patients, paranoid schizophrenic patients demonstrated specific abnormalities in neural responses to threatening facial expressions, i.e. facial expressions of fear and anger, perhaps due to abnormal activation to neutral stimuli. Non-paranoid schizophrenic patients demonstrated abnormal neural responses to all types of negative facial expression (8) resulting from a dysfunctional association process between exteroceptive sensory inputs and interoceptive changes (11).

Failure to activate limbic regions during emotional valence discrimination was shown again in Gur et al. (2002) study (4). In this work, schizophrenic patients showed reduced activation of the left amygdala and bilateral hippocampus in response to the explicit task requiring discrimination of facial positive from negative affect. These results may explain emotion processing deficits in patients with schizophrenia (4).

Contrast pattern of results was obtained by Kosaka et al. (2002), who conducted fMRI study in healthy controls and schizophrenics using emotional intensity judgment task (6). Negative face discrimination activated the bilateral amygdalae in schizophrenia, whereas the

right amygdala alone was activated in controls. The authors attempted to explain exaggerated amygdala activation found in schizophrenia by impaired gating of sensory input containing emotion (6). Interestingly, Parker et al. (2001) showed marked amygdala activation in paranoid schizophrenics in response to ambiguous stimuli comprising fearful faces and neutral sounds but not in response to fearful facial expressions and fearful sounds (7).

Similar findings were obtained by Russell et al. (2002) (paper in preparation), who used facial experiment based on "intensity changing". In this task the subject was presented with a neutral face that increments by 10% into a prototypic expression (100%) over a 10 second period. The face "changes" or increments by 10% every 1000 milliseconds. When the face had reached 100% of the expression (alternating blocks of fear and neutral faces) the subject decided only the sex of each face. Generic brain activation analysis revealed an enhanced left amygdala response to such stimuli, whereas consecutive experiment consisting of blocks of neutral faces and 100% fearful faces (8) failed to activate limbic structures in schizophrenia. These regent findings reflect functional amygdale abnormalities in overt displays of fear in schizophrenic patients. Lack of amygdala activation in obvious aversive stimuli and enhanced amygdalar response to ambiguous stimuli might be explained by an altered treshold at which the amygdala responds to fearful stimuli. The changes of vigilance and attentive processes to fearful information by amygdala might be enhanced in schizophrenia (9).

STRUCTURAL AMYGDALA CHANGES IN SCHIZOPHRENIA

There is now overwhelming evidence of structural brain abnormality in schizophrenia. The resolution of structural magnetic resonance imaging (MRI) is sufficient to enable quantitative assessment of the volume of the amygdala complex, although the individual nuclei that comprise this heterogeneous structure are not distinguishable. Moreover, because the amygdala borders are not all clear owing to the proximity to other grey structures, most methodologies rely on external landmarks and stereotactic methods to improve reliability (3). Medial temporal lobe structures such as the amygdala and hippocampus are the most frequently observed in schizophrenic patients.

Table 2. Structural changes of amygdala-hippocampal complex (A-H) in schizophrenia: review of recent volumetric magnetic resonanse imaging

MRI study	Key findings
DeLisi et al. 1997	Longitudinal study – no changes over 4 years in A-H complex or in temporal lobe volume
Sanderson et al. 1999	Brain volumes of schizophrenic group with intellectual disability were smaller, although their A–H complexes were relatively larger
Gur et al. 2000	Amygdala volume reduction in male schizophrenic patients
Rajarethinam et al. 2001	No significant reduction of amygdala volume after adjusting for total brain volume was found in schizophrenia. Inverse correlation between LA and thought disorder was found
Levitt et. al. 2001	After adjustment for age and total brain volume, the left amygdala was significantly larger in childhood-onset schizophrenia than in the control subjects
Chance et al. 2002	No significant reduction of amygdala volume was found in schizophrenia (post-mortem study)
Sumich et al. 2002	Paranoid patients had smaller left amygdala volume relative to non-paranoids

Morphological change of bilaterally amygdala volume has been found using MRI (13) although some researchers have found only unilateral reduction or enlargement in the left amygdala (Tab.2). Moreover, first-degree relatives of schizophrenia patients revealed signifycant volume reductions bilaterally in the amygdala-hippocampal complex (14), whereas decreased left amygdala and hippocampal volumes were shown in young offspring of schizophrenia patients which might suggest a neurodevelopmental origin of such changes (5).

In contrast, the post-mortem studies (Tab. 2) found unchanged amygdala volume in schizophrenia, which might suggest that schizophrenia does not affect all limbic structures equally, or highlight the key problem as anatomical definition of amygdala in vivo- and post-mortem studies.

STABILITY AND DURABILITY OF AMYGDALA STRUCTURAL ABNORMALITIES

The relationship between structural abnormalities and clinical variables or the deficits at the behavioural and physiological (functional) level in schizophrenia has yet to be clarified. A number of studies have focused on amygdala as a possible key site of pathology. The inverse correlation with left amygdala volumes and thought disorder quantified using Brief Psychiatric Rating Scale was found (Tab. 2). Furthermore, Sanderson et al. (2001) showed small amygdalo-hippocampal size to be associated with history of Centrous Nervous System injury, particularly meningitis in schizophrenia (10). In terms of durability of abnormalities in amygdala-hippocampal volume they appear not to change over time (Table 2).

Pioneering work of Shaw et al. (2003) showed the impact of the volume of the amygdala on its activation during the processing of facial expressions of fear (13). They proved that the amygdala could be reliably measured on high resolution GE images with the volumes obtained correlating significantly with those obtained from an anatomical 'gold standard' sequence. For both healthy controls and subjects with schizophrenia there was a positive correlation between the total volume of the amygdala estimated from the GE sequences and number of pixels activated in the amygdala (13).

CONCLUSIONS

Understanding of the neuropathology of schizophrenia with particular focus on amygdala as a key site of such pathology has increased dramatically over the past decade. However, brain imaging literature on amygdala abnormalities in schizophrenia is full of inconsistencies due to incomplete understanding of the illness itself, different techniques and stimuli used. Further exploration in this field of research with close psychometric matching of prosodic and facial affect tasks and using similar neuroimaging acquisition would be valuable to obtain convergent conclusions.

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SUMMARY

Despite the evidence for impaired perception of negative affect in schizophrenia, there have been a few functional neuroimaging studies so far examining neural responses to facial negative emotional stimuli in this illness. These studies have demonstrated that schizophrenic patients relative to healthy controls fail to activate the amygdala in response to facial expressions of fear, and also during a sadness induction paradigm. These recent findings reflect functional amygdala abnormalities in overt displays of fear in schizophrenic patients. Lack of amygdala activation in obvious aversive stimuli and enhanced amygdalar response to ambiguous stimuli might be explained by an altered treshold at which the amygdala responds to fearful stimuli. Morphological change of bilaterally amygdala volume has been found using MRI although some researchers have found only unilateral reduction or enlargement in the left amygdala. To conclude, brain imaging literature focused on amygdala abnormalities in schizophrenia is full of inconsistencies due to incomplete understanding of the illness itself, different techniques and stimuli used.

Percepcja negatywnych emocji w schizofrenii – funkcjonalne i strukturalne zmiany ciała migdałowatego. Przegląd badań

Pomimo istnienia dowodów na istnienie w schizofrenii zaburzeń percepcji informacji o negatywnym zabarwieniu emocjonalnym wykonano jedynie kilka badań neuroobrazujących,

oceniających funkcjonalną aktywność mózgu w odpowiedzi na zaproponowane bodźce emocjonalne w tej chorobie. Te badania wskazały brak aktywacji ciała migdałowatego u chorych na schizofrenię w odpowiedzi na prezentację twarzy wyrażających strach jak również w eksperymencie indukowania smutku. Odzwierciedla to czynnościowe anomalie ciała migdałowatego w odpowiedzi na silnie awersyjne bodźce w schizofrenii. Brak uaktywniania ciała migdałowatego i jednocześnie jego nadmierna aktywacja w odpowiedzi na niejednoznaczną emocjonalną informację można tłumaczyć zmienionym progiem aktywacji ciała migdałowatego w schizofrenii pod wpływem strachu. Strukturalne zmiany w obustronnej objętości ciała migdałowatego zostały potwierdzone w badaniach przy użyciu MRI, chociaż kilka badań wskazuje na lewostronne występowanie tych anomalii. Podsumowując, literatura dotycząca badań neuroobrazujących ciała migdałowatego w schizofrenii nie potwierdza zgodnych wniosków. Uzasadnieniem tej prawidłowości może być brak pełnego zrozumienia złożonej natury procesu schizofrenicznego, zastosowanie różnorodnych technik neuroobrazujących, jak i różnych eksperymentów badawczych.