Fornix & Stria Terminalis

Virtual Neuroanatomy
10/21/2014
Background: Limbic System

Interconnected cortical and subcortical regions that link visceral states and emotion to cognition and behavior.

Catani et al. 2013
Interconnected cortical and subcortical regions that link visceral states and emotion to cognition and behavior.
Background: Visceral Regulation

Neuroendocrine

- Hypothalamus
- Capillary beds
- Anterior lobe of pituitary
- Hormone-secreting cells

- Parvicellular neurosecretory cells
- Hypophyseotropic hormones released
- Stimulation or inhibition of anterior pituitary hormone release
- Hormone in blood
- Action on organs of the body

Autonomic

- Hypothalamus
- Capillary beds
- Anterior lobe of pituitary
- Hormone-secreting cells

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- Stimulation or inhibition of anterior pituitary hormone release
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Background: Key Limbic Regions are Visceral

- Hypothalamus
- Amygdala
- Brainstem

BODY
Background: The Fornix

One of the first PET studies looking at the functional anatomy of the 'default networks' (Shulman et al., 1997). Area 1 corresponds to the posterior cingulate cortex/precuneus and area 9 to the anterior cingulate/medial frontal cortex. These two areas are interconnected through the dorsal fibres of the cingulum. Notwithstanding this, the volume of the cingulum is bilateral and symmetrical in most subjects (Thiebaut de Schotten et al., 2011b).

2.5. Uncinate

The uncinate fasciculus connects the anterior part of the temporal lobe with the orbital and polar frontal cortex (Fig. 8). The fibres of the uncinate fasciculus originate from the temporal pole, uncus, parahippocampal gyrus, and amygdala, then after a U-turn, enter the floor of the extreme capsule. Between the insula and the putamen, the uncinate fasciculus runs inferior to the fronto-occipital fasciculus before entering the orbital region of the frontal lobe. Here, the uncinate splits into a ventro-lateral branch, which terminates in the anterior insula and lateral orbitofrontal cortex, and an antero-medial branch that continues towards the cingulate gyrus and the frontal pole (Crosby et al., 1962; Dejerine, 1895; Klingler and Gloor, 1960).

Whether the uncinate fasciculus is a lateralised bundle is still debated. An asymmetry of the volume and density of fibres of this fasciculus has been reported in a human post-mortem neurohistological study in which the uncinate fasciculus was found to be asymmetric in 80% of subjects, containing on average 30% more fibres in the right hemisphere compared to the left (Highley et al., 2002). However, diffusion measurements have shown higher...
Background: Another limbic bundle -- Stria Terminalis

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Background: BNST is Visceral, too
Fornix: Afferents/Efferents

Hippocampus:
10 – Subiculum
12,14,15 – Ammon’s Horn/Cornu Ammonis

Nieuwenhuys 2007

Bruni and Montemurro 2009
Fornix: Afferents/Efferents

Bruni and Montemurro 2009
Fornix: Afferents/Topography

1. Precommissural fornix – septal area, basal and medial forebrain, hypothalamic areas

2. Postcommissural fornix – mammillary bodies; anterior and midline thalamus; bed nucleus of the stria terminalis

Nieuwenhuys 2007
Fornix: Afferents/Topography

1. Septo-hippocampal (precommissural fornix) - ventricular

2. Commissural projections (dentate gyrus/CA3 efferents) – ventral hippocampal commissure (VHC)/pial surface

3. Entorhinal cortex (crossed) - ventricular

Adelmann et al. 1996

Nieuwenhuys 2007
Fornix: Neurophysiology/Neurochemistry

Adelmann et al. 1996
Ultrastructure of synapses in the fimbria, a
Electron micrograph of the dorsal fimbria. Several axon terminals form synapses with a dendrite (D) of an unidentified target neuron. The arrows point to the synaptic clefts.

Electron micrograph of the caudal (posterior) fimbria. Numerous axon terminals form synapses with dendrites. The bold arrows indicate the synaptic clefts. One terminal contains dense core vesicles (open arrows).

Bar 2 gm in a, 1 gm in b

Adelmann et al. 1996
Fornix: Behavioral Correlates

Memory

Fornix appears to be necessary for memory (acquisition and retention). (Sutherland and Rodriguez 1989, Galani 2002, Cassel 1998, Nilsson 1987)

![Graph showing mean number of errors in first eight choices across trials for different groups: Control, Fornix, Caudate.](Packard et al. 1989)
Fornix: Behavioral Correlates

Fear Conditioning

CS

Freezing (sec)

Day

1 2 3

Control Fornix

Context

Control Fornix

Phillips and LeDoux 1995
Fornix: Physiological Correlates

Corticosterone (Neuroendocrine) Response to Operant Conditioning

An analysis of variance of these data yielded a significant effect of treatment ($F = 20.7, p < 0.001$) and a significant treatment by lesion interaction ($F = 4.95, p < 0.005$). Both groups were responsive to experimental manipulations, but the response profiles of control and lesioned animals differed. In order to specify more precisely the nature of the differences in profile, within group comparisons for individual treatments were made using Newman-Keuls comparisons ($p < 0.05$); these are summarized at the top of the figure.

Starting from the nondeprived condition (B) which represents the nonstressed diurnal baseline level, control rats responded to each additional stimulus with a significant increase in corticosterone.
Fornix: Physiological Correlates

• Stimulation in humans with involuntary movement problems (Doi et al. 1968)
  – ~2 degree decrease in body temperature
  – Flushing/perspiration
  – Dilated pupils

• Stimulation of dorsal fornix in rabbits (Cragg and Hamlyn 1959)
  – Decreased blood pressure
  – Increased respiration
Fornix: Physiological Correlates

Fornix transection made rats resistant to high glucocorticoid feedback signal (Sapolsky et al. 1989)
Fornix: Clinical Pathologies
Temporal Lobe Epilepsy

Epilepsy patient

Normal autopsy

Myelin degeneration (thick arrow) whereas non-epileptic autopsies (Fig. 2 a), whereas non-epileptic autopsies showed no statistically significant difference in myelinated and unmyelinated fibers of the right fornix only (Fig. 2 b).

The total number of fornix fibers was always greater on the right side and the mean total number of fibers was higher in epileptic autopsies for both right (p = 0.043) and left (p = 0.021) sides compared with non-epileptics. However, the reduction was statistically significant for the unmyelinated fibers of the right fornix only (p = 0.029).

Statistical analysis was by use of the Mann–Whitney U test. The mean number of fornix fibers was significantly lower in the epileptic autopsies for both right (p = 0.043) and left (p = 0.021) sides compared with non-epileptic autopsies (Table 2).

Ozdogmus et al. 2009
reduced myelin fraction (positive correlation with the cumulative axonal membrane circumference tended to be lower in the TLE patients such as separation of myelin layers. Both groups showed differences in axonal diameters.

Between the two TLE groups, with TLE and thus axonal density (fractional anisotropy), the extra-axonal fraction best differentiated between TLE patients such as separation of myelin layers. Both groups showed differences in axonal diameters.

Mean electron microscopy blinded measurements per group are taken from the average features over 10 stereology frames per subject. Numbers in parentheses represent SEM.

<table>
<thead>
<tr>
<th></th>
<th>TLE+uMTS</th>
<th>TLE-MTS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelin fraction</td>
<td>0.12 (0.01)</td>
<td>0.15 (0.02)</td>
<td>0.012</td>
</tr>
<tr>
<td>Cumulative axon membrane circumference</td>
<td>0.67 (0.07)</td>
<td>0.72 (0.13)</td>
<td>0.4</td>
</tr>
<tr>
<td>Myelin thickness (nm)</td>
<td>186 (13)</td>
<td>194 (25)</td>
<td>0.53</td>
</tr>
<tr>
<td>Axonal density (axons/mm²)</td>
<td>164 (13)</td>
<td>205 (39)</td>
<td>0.035</td>
</tr>
<tr>
<td>Inner axonal diameter (μm)</td>
<td>0.61 (0.02)</td>
<td>0.67 (0.07)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Discussion

Electron microscopy and tractography of the fimbria-fornix. Histological fields of the fimbria-fornix resected during epilepsy surgery from two representative patients with TLE are shown with their corresponding axial FA maps (Concha et al., 2005b, 2006; Mac Donald et al., 2007). We demonstrated a trend that fractional anisotropy did not show any significant correlation with myelin thickness, whereas mean, parallel, and perpendicular diffusivities did not show any significant correlation with any of the histological features derived from electron microscopy of a small specimen of the fimbria-fornix marked as green and tractography of the fimbria-fornix (D). This corresponds to lower axonal density of the fimbria-fornix. Given a negative correlation with the cumulative axonal membrane circumference, the patient with mesial temporal sclerosis (Patient 8) (B) shows a negative correlation with myelin thickness (nm) and higher extra-axonal fraction (fractional anisotropy) than in the subject with TLE (A).

The patient with mesial temporal sclerosis (Patient 8) (B) shows a negative correlation with myelin thickness (nm) and higher extra-axonal fraction (fractional anisotropy) than in the subject with TLE (A). The patient with mesial temporal sclerosis (Patient 8) (B) shows a negative correlation with myelin thickness (nm) and higher extra-axonal fraction (fractional anisotropy) than in the subject with TLE (A). The patient with mesial temporal sclerosis (Patient 8) (B) shows a negative correlation with myelin thickness (nm) and higher extra-axonal fraction (fractional anisotropy) than in the subject with TLE (A).

Concha et al., 2010
Fornix: Clinical Pathologies

Cognitive Deficits: Alzheimer Disease

lobes, and critically the columns of the fornix may result in devastating behavioral alteration with features of abulia (poverty of speech and emotional apathy), severe anterograde amnesia and, particularly in the case of cingulate involvement, hypersexuality and agitation.

DWI is clearly critical in stroke evaluation, allowing for detection of infarction within minutes of onset and providing reasonable estimation of age of infarct in patients with delayed presentation.

Transient Global Amnesia
This distinct, short-lived amnestic syndrome remains of unknown etiology, although occasionally, DWI-hyperintense lesions are encountered in the hippocampus, leading many to conclude a probable vascular etiology.

Subacute presentations should prompt consideration of inflammatory or infectious causes. The infection that appears to show a particular tropism for the limbic system is herpes simplex (types 1 and 2). The typical presentation is with fever, confusion, and seizures. CT may show low density in the temporal lobes, but MRI is the most sensitive way of detecting subtle or early changes. There is T2 and FLAIR cortical or gray matter hyperintensity in the amygdala and hippocampus (often bilaterally). Detecting involvement of the insula and anterior cingulate cortex is helpful in unilateral cases to help suggest infection rather than tumor. Lesions may often be hemorrhagic and show contrast enhancement. DWI is sensitive at showing regions of involvement before T2-FLAIR signal alteration develops.

Amore prolonged presentation tends to occur with autoimmune limbic encephalitis. This may be idiopathic but is frequently associated with an underlying systemic malignancy. The antibodies detected may help in directing the search for an underlying lesion: anti-Hu antibodies are associated with small cell lung cancer, anti-N-methyl-D-aspartate receptor antibodies with ovarian teratomas, and anti-Ma2 antibodies with testicular germ cell tumors. Anti–voltage-gated potassium channel antibodies are associated with thymic tumors. Imaging findings in limbic encephalitis may overlap with herpetic infection with bilateral T2-FLAIR-hyperintense swelling of the hippocampi and amygdala. A more symmetrical pattern of involvement and lack of meningeal enhancement, along with clinical features, may act as a clue to autoimmune rather than infectious etiology.

Cognitive Impairment
Given its role in memory formation, any disease that affects the hippocampus may present with problems with short-term memory in particular. Alzheimer disease affects the hippocampi preferentially, and although disproportionate hippocampal atrophy may be demonstrated on standard structural imaging, these features may not be apparent until late in the course of disease. In addition to focal atrophy, functional studies such as positron emission tomography perfusion scanning may show temporal hypoperfusion and new ligands such as Pittsburgh Compound B allow detection of abnormal amyloid deposition.

Figure 17 Alzheimer disease: (A) series of 18FDG-PET images showing bilateral temporal lobe hypoperfusion (arrows); (B) axial T2-weighted image of the brain showing diffuse cortical atrophy; (C) coronal T1 image showing advanced bilateral hippocampal atrophy (arrows); (D) arterial spin-labeling (ASL) perfusion imaging also shows the temporal lobe hypoperfusion (arrows). 18FDG-PET, fludeoxyglucose-positron emission tomography.
Stria Terminalis: Afferents/Efferents

Amygdala (12-17):
12 – Cortical
13 – Anterior
14 – Lateral
15 – Central
16 – Medial
17 – Basal
Stria Terminalis: Afferents/Topography

1. Precommissural/ supracommissural/dorsal
2. Commissural
3. Postcommissural/ preoptic/ventral
1. Precommissural/supracommissural/dorsal – olfactory areas, nucleus accumbens, BNST, ventromedial hypothalamus
2. Commissural – contralateral BNST
3. Postcommissural/preoptic/ventral – ventromedial hypothalamus
Stria Terminalis: Topography, Amygdala-to-BNST

A. Organization of the stria terminalis

Sources of fibers: 1. CEAm, 2. BMAa, 3. COAa, 4. BLAp, 5. TR, 6. I

Dong and Swanson 2001
Fig. 36. The BST viewed in the context of a standard cortico–striatopallidal projection system. (A) In a prototypical or minimal cortico–striatopallidal projection (using the isocortex–dorsal striatum–globus pallidus as a model), layer 5 of cortex sends a glutamatergic projection to the motor system in the brainstem and/or spinal cord, with a collateral to the striatum; the striatum sends a descending GABAergic projection to the brainstem motor system, with a collateral to the pallidum; and the pallidum also sends a GABAergic projection to the brainstem motor system, and a collateral to thalamocortical re-entrant loops (see [101]). As discussed in the text, most of the BST (except perhaps certain anterolateral regions) fit nicely into this connectional scheme, as a rostral component of the pallidum. (B) There are a number of other connections arising within the cerebral hemispheres that supplement the basic circuitry outlined in A. As discussed in the text, additional connections such as these are also found in other regions of the striatopallidum. Projections from presumed cortical subplate regions of the amygdala to presumed striatal regions of the amygdala are discussed in Refs. [12,75,83]. In parts A and B, projections shown in red are GABAergic, and presumably inhibitory (or disinhibitory in the case of pallidal structures); whereas projections shown in black are glutamatergic and presumably excitatory.

It has also been suggested that reciprocal connections characterize specific pairs of cell groups in the central/medial nuclei and BST (e.g., [2,3,27]). However, in two exceptions. For example, the central and medial nuclei receive massive inputs from the lateral, anterior basolateral nuclei of the amygdala (Fig. 3). The second example involves the distinctive juxtacapsular nucleus of the BST. It projects heavily to the medial part of the central amygdalar nucleus [30] but receives no input from any part of the central or medial nucleus of the amygdala (Fig. 3). The second example involves the distinctive oval and fusiform nuclei, also in lateral regions of the BST. Both nuclei receive inputs from all three parts of the central amygdalar nucleus (Fig. 3), but each nucleus projects back selectively to the medial rather than lateral part of the central nucleus [31]. Related suggestions that corresponding parts of the central/medial amygdala and BST share similar inputs and outputs has not been subjected to detailed analysis, but there are obvious exceptions. For example, the central and medial nuclei of the BST have corresponding subdivisions in the lateral and medial amygdala, respectively (e.g., [2,3,27]). However, first example involves the distinctive juxtacapsular nucleus of the BST. It is apparent from Fig. 3 that projections arising in the far lateral BST. It projects heavily to the medial part of the central amygdalar nucleus [30] but receives no input from any part of the central or medial nucleus of the amygdala (Fig. 3). The second example involves the distinctive oval and fusiform nuclei, also in lateral regions of the BST. Both nuclei receive inputs from all three parts of the central amygdalar nucleus (Fig. 3), but each nucleus projects back selectively to the medial rather than lateral part of the central nucleus [31]. Related suggestions that corresponding parts of the central/medial amygdala and BST share similar inputs and outputs has not been subjected to detailed analysis, but there are obvious exceptions. For example, the central and medial nuclei of the BST have corresponding subdivisions in the lateral and medial amygdala, respectively (e.g., [2,3,27]). However, first example involves the distinctive juxtacapsular nucleus of the BST. It is apparent from Fig. 3 that projections arising in the far lateral BST. It projects heavily to the medial part of the central amygdalar nucleus [30] but receives no input from any part of the central or medial nucleus of the amygdala (Fig. 3). The second example involves the distinctive oval and fusiform nuclei, also in lateral regions of the BST. Both nuclei receive inputs from all three parts of the central amygdalar nucleus (Fig. 3), but each nucleus projects back selectively to the medial rather than lateral part of the central nucleus [31]. Related suggestions that corresponding parts of the central/medial amygdala and BST share similar inputs and outputs has not been subjected to detailed analysis, but there are obvious exceptions. For example, the central and medial nuclei of the BST have corresponding subdivisions in the lateral and medial amygdala, respectively (e.g., [2,3,27]). However, first example involves the distinctive juxtacapsular nucleus of the BST. It is apparent from Fig. 3 that projections arising in the far lateral BST. It projects heavily to the medial part of the central amygdalar nucleus [30] but receives no input from any part of the central or medial nucleus of the amygdala (Fig. 3).
Neuropeptide-containing pathway:
- Enkephalin (Uhl 1978)
- Neuropeptide-Y (Allen 1984)
- Neutotensin (Uhl 1979)
- Sensitive to estrogen and testosterone (Takeo 1995, Kendrick 1979)
Stria Terminalis: Behavioral Correlates

Memory

When memory is modulated experimentally (epinephrine, glucocorticoids, cholecystokinin, etc.) ST lesions block or facilitate those effects (Torras-Garcia 1998, Packard 1996, Roozendaal 1996, Flood 1995)
Stria Terminalis: Behavioral/Physiological Correlates

Homeostatic functions

• Food intake
  – Bilateral transections induce weight gain in female rats (King et al. 2003, Rollins 2006)

• Sexual activity
  – Lordosis in females (Takeo 1995)
  – Copulatory behavior in males (Lehman 1983, Tsutsui 1994))

• Neuroendocrine function
  – ST lesions completed inhibit adrenocortical responses to olfactory stimulation (Feldman and Conforti 1980)
Stria Terminalis: Clinical Pathologies

Translational Implications of the Amygdala–Stria Terminalis Model for the Clinical Anxiety Disorders

Ballenger 1989

Double Dissociation Studies
Michael Davis

Light-enhanced startle – Acoustic startle response enhanced in the presence of bright light
*Unconditioned Fear*

Fear-potentiated startle – Acoustic startle response enhanced in the presence of cues previously paired with shock – *Conditioned Fear*
Stria Terminalis: Clinical Pathologies

Central Amygdala Lesions

(A) Light-enhanced Startle
- Dark phase
- Light phase
- Difference

(B) Fear-potentiatiated Startle
- Startle stimulus alone
- Light CS & startle stimulus
- Difference

BNST Lesions

(B) Light-enhanced startle - Delayed

(C) Fear-potentiatiated startle

Walker and Davis 1997

Results from the central nucleus of the amygdala and bed nucleus of the stria terminalis. These scores were then calculated from a subset of animals that received NBQX during both procedures. To confirm this statistically, we performed a paired t-test comparing the mean light difference scores of rats that received NBQX during light-enhanced startle. This was done to determine if there was a significant difference in the startle amplitude of NBQX- and PBS-infused rats. The mean light difference scores for rats that received NBQX during light-enhanced startle were significantly greater than those for rats that received PBS. This indicates that NBQX infusions into the bed nucleus of the stria terminalis block fear-potentiated startle, there was also no apparent relation between can-

For central nucleus implants, fear-potentiated startle difference scores were calculated by dividing the mean fear-potentiated startle amplitude of NBQX-infused rats by the mean fear-potentiated startle amplitude of PBS-infused rats. Similarly, light-enhanced startle difference scores were calculated by dividing the mean light-enhanced startle amplitude of NBQX-infused rats by the mean light-enhanced startle amplitude of PBS-infused rats. For both protocols, there was no apparent relation between changes in startle amplitude and drug treatment. Thus, NBQX infusions into the bed nucleus of the stria terminalis block fear-potentiated startle, there was also no apparent relation between can-

Double dissociation

These findings indicate similarities as well as differences in the role of the central nucleus of the amygdala and to the bed nucleus of the stria terminalis. These scores were then calculated from a subset of animals that received NBQX during both procedures. To confirm this statistically, we performed a paired t-test comparing the mean light difference scores of rats that received NBQX during light-enhanced startle. This was done to determine if there was a significant difference in the startle amplitude of NBQX- and PBS-infused rats. The mean light difference scores for rats that received NBQX during light-enhanced startle were significantly greater than those for rats that received PBS. This indicates that NBQX infusions into the bed nucleus of the stria terminalis block fear-potentiated startle, there was also no apparent relation between can-

Figure 6. Effect of NBQX on light-enhanced startle. There was a statistically significant session type effect (F0.05), indicating an overall effect of treatment (H0.05). Thus, NBQX attenuated the phase I to phase II increases (A). There was not, however, a significant session type effect (F0.05) on dark sessions did not replicate, allowing for a more specific attribution of the effects of NBQX to a disruption of light-enhanced startle. There was a statistically significant session type effect (B). There was a statistically significant session type effect (C).
Stria Terminalis: Clinical Pathologies

Because BNST lesions abolish Light-Enhanced Startle, which is unconditioned, it is thought to be more relevant to Generalized Anxiety Disorders, whereas Amygdala (central and basolateral nuclei) may be more relevant to disorders like PTSD.

*Implicates Stria Terminalis in anxiety disorders*