

- Outline
- Review methods for studying white matter anatomy and brain connectomics
- Functional neuroanatomy of: Projection Tracts Association Tracts Commissural Tracts
- Functions and clinical correlates







#### **Clinical Importance of White Matter**

- Many diseases impact brain white matter integrity or have white matter underpinnings
   Multiple Scierosis
   Stroke
   Amyotrophic Lateral Scierosis
   Epilepsy
   Neurodegenerative
   Traumatic Brain Injury
   Neurodevelopmental Disorders
   Psychiatric Disorders
   Psychiatric Disorders
   Neurourgical nanning

  - Neurosurgical planning And many more ......



White matter injury conceptualized as a subcortical cognitive picture but more nuanced and varied than this



#### **Gross Dissection**

- Klingler Technique (1930s)
- Fix brain in formalin
  Freeze brain at low temp
- Thaw brain
- Peel away cortex
- Peel away white matter fibers parallel to axonal direction



7

#### Diffusion MRI (dMR)

- Quantitative analysis of magnitude and directionality of water molecules
- Water molecules present with random thermally driven motion Brownian motion



8

#### **Color Coded FA Maps**



Transverse (x axis) Superior Inferior (z axis) Anterior Posterior (Y axis)

Intensity of color = fractional anisotropy magnitude



#### **MR Tractography**

- Tractography algorithms used to reconstruct white matter tracts based on diffusion data 0
- Different techniques and algorithms with different assumptions-streamline/deterministic vs -probabilistic



10

#### **Resting State fMRI**

- · Examines the correlations between spontaneous fluctuations in the BOLD signal across brain regions while subject at rest
- Functional connectivity is related to structural connectivity but there are cases of indirect connectivity pathways via mediating region (region A goes through B to influence C)
- Different methods for examining connectivity
  - Functional Connectivity Density Analysis
     Seed Based Functional Connectivity

  - Independent Component Analysis
  - Graph Theory

Anatomical connectivity – dMRI

11

#### **Electrical Stimulation**

- Deliver electrical current to disrupt underlying brain tissue
- Allows direct confirmation whether an area is necessary to a given function
- · Allows for testing of subcortical white matter functions



#### **Cortico-Cortico Evoked Potentials (CCEPs)**

- Stimulate one cortical area and record the evoked responses in other cortical areas via intracranial electrodes (sEEG)
- Allows evaluation of connectivity through directional and time resolved data



13

Infer tract function by understanding the functions of the connected brain regions



14

#### White Matter Tract Classification

#### Projection Fibers

- Connects cortex with lower parts of the brain (thalamus, pons) and spinal cord
- $-\,$  e.g., cortico-spinal, bulbar, pontine tracts, optic radiations

#### Association Fibers

- Connects various portions of cortex to cortex
- Short association U fibers connect adjacent gyri
   Long fibers connect distant parts
- Long inders connect distant par
   e.g., SLF, AF, IFOF, ILF, MLF, UF
- e.g., SLF, AF, IFOF, ILF, MLF, OF

#### Commissural Fibers

- Connects the two cerebral hemispheres
- e.g., corpus callosum, anterior/posterior commissure, hippocampal commissure

#### White Matter Regions

#### Centrum Semiovale

- Sheet of white matter containing projection and association fibers
- Located <u>above</u> level of lateral ventricles & CC
- Continues ventrally into corona radiata
- Contains mostly CST

#### Corona Radiata

- Sheet of white matter at the level of lateral ventricles that continues inferiorly into internal capsule
   Containe participation bullbac and oping!
- Contains corticopontine, bulbar and spinal tracts









#### **Cortical Motor Areas: Quick Review**















#### **Corticospinal Tract (CST)**

- Originates in the pre and post central gyrus
- Converges and travels down through the corona radiata
   A-P: face, leg/foot
- Into the posterior internal capsule
   AP: face, hand, foot
- Into cerebral peduncles
   LM: leg, hand, face
- To the medulla crossing over at the pyramidal decussation
- Into the spinal cord







#### **Corticobulbar Tract**

- Originates in the precentral gyrus (mainly in face motor area)
- Travels down through the corona radiata into the genu of the internal capsule running mediodorsal to the CST at the level of cerebra peduncles
- Terminates in CN nuclei in brainstem (trigeminal, facial, vagus, hyoglossal, spinal accessory nerves)





#### Corticopontine Tract

- Originates in the pre and post central gyrus, as well as parietal, temporal and occipital lobes
- Substantial contributions from premotor, SMA, posterior parietal cortices
- Travels down through the corona radiata into the anterior limb of the internal capsule and medial cerebral peduncles
- Terminates into pontine nuclei
- Second order nuclei project into cerebellum via cerebellum peduncle







33

#### **Clinical Correlates**

- Damage to CST affects contralateral voluntary movements and can result in weakness, spasticity, and hyperreflexia in the limbs and trunk
- Damage to the corticobulbar tract can result in pseudobulbar palsy (slow speech, dysphagia, dysarthria, spastic tongue), contralateral lower facial droop and weakness in hypoglossal muscles
- Damage to corticopontine tract can result in balance issues manifesting as ataxia, dysmetria, tremor, problems with rapid alternating movements

#### Lesion Localization

- Patient presents with acute onset left arm, hand, and face weakness but no leg weakness. Where is the lesion? What vascular supply?
- Patient presents with acute onset left leg but no arm or face weakness. Where is the lesion? What vascular supply?

Patient presents with acute onset left hemibody (arm, face, leg) weakness. Where is the lesion? What vascular supply?

35





#### Extreme Capsule

- Lateral to external capsule
- Long association fiber pathway of white matter in the brain that provides bidirectional communication between such areas as the claustrum and the insular cortex, and the inferior frontal gyrus and the middleposterior portion of the superior temporal gyrus
- Bottle neck IFOF, UF, T-F Extreme Cap Fasciculus
- Implicated in language; Left sided damage can result in aphasia







#### **External Capsule**

- Runs between lateral lentiform nucleus and claustrum
- Contains cortico-cortico association fibers



42















#### **Closer Look at the Optic Radiations**



48



49

#### **Closer Look at the Optic Radiations**

- Geniculocalcarine tract connects the LGB to the primary visual cortex and contains 3 components

  - components
    Dorsal Bundle extends directly posterior to meet the upper part of calcarine fissure
    Central Bundle leaves LGB in a lateral direction and tracks posteriorly along LV all to visual cortex
    Meyers Loop projects from LGB and runs anteriorly across the top of the temporal horn then turns sharply to run posteriorly along wall of LV to the inferior calcarine fissure

A. Mandektam. Challenges of the Anatomy and Diffusion Tensor Tractography of the Meyer Loop merican Journal of Neuroradiology Aug 2012, 33 (7) 1204-1210; DOI: 10.3174/ajnr.A2652











#### Fornix

- C-shaped bundle that connects the hippocampus to the mammillary bodies and anterior nucleus of the thalamus
- · It is the primary pathway out (efferent) of the hippocampus
- Components of the Fornix:
  - mponents of the Fornix: Fimbria attaches to body and tail of hippocampus, runs along medial edge of hippocampus Crus trails off hippocampus Body both sides join beneath the splenium of the CC, arching over the thalamus Columns descend into forebrain, split around the anterior commissure, extends to mammillary bodies





#### **Function and Clinical Correlates**

- · Fornix is important in the formation and consolidation of declarative memories
- Damage to the fornix can result in anterograde amnesia mirroring hippocampal lesions disconnection syndrome
   Midline tumors (e.g., colloid cyst), TBI, HSE, WKS, MCIa & Alzheimer's disease
- · Material specificity to memory impairment with unilateral damage (left verbal, right - visual)
- · Confabulation not typical like in diencephalic amnesia
- Correlations between fornix integrity as measured by DWI and episodic memory performance across a range of ages and tasks
- · Mechanism transmit acetylcholine from basal forebrain to hippocampus

Benear SL, Ngo CT, Olson IR. Dissecting the Fornix in Basic Memory Sep;10(7):331-354. doi: 10.1089/brain.2020.0749. Epub 2020 Jul 21. e:AR

57



58

#### Superior Longitudinal Fasciculus (SLF)

• SLF divided into 3 segments: SLF 1, 2 & 3



#### Superior Longitudinal Fasciculus (SLF 1)

- Run in the AP direction within the superior frontal gyrus
- Connects superior parietal lobule (BA 7) and precuneus to the superior frontal lobe (BA 6, 8 & 9) and anterior cingulate cortex and SMA



60

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61

#### Superior Longitudinal Fasciculus (SLF 1)

- Likely functions in higher-order control over body-centered action and may be a major white matter connection in the default mode network
- Right SLF 1 implicated in visuospatial attention and voluntary orienting of spatial attention/goal directed attention (top down, dorsal attention network)

Ribeiro, Yordanka Nikolova Yordanova, Vincent Noblet, Guillaume Herbet, Damier and correlation evidence, *Brain*, Volume 147, Issue 2, February 2024, Pages 352–37.

- Left SLF 1 may support verbal working memory while right SLF 1 may support visual working memory

#### Superior Longitudinal Fasciculus (SLF 2)

- SLF 2 runs parallel to SLF 1 and connects the occipital (BA 19) and regions around the intraparietal sulcus to the dorsolateral prefrontal cortex (BA 46)
- Largely lies in the MFG



63

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64

#### Superior Longitudinal Fasciculus (SLF 2)

- Possible role in semantics in left hemisphere
- Right SLF 2 supports visual working memory
- May mediate interactions between dorsal and ventral attention systems with damage to right SLF 2 being associated with left neglect
- SLF2 & SLF 3 support flexible responses and inhibition
   In surgical sample, damage associated with TMT B and Stroop performances

licard, White matter tracts and executive functions: a re



#### Superior Longitudinal Fasciculus (SLF 3)

- SLF 3 connects the supramarginal gyrus (BA 40) to pars operculum (BA 44) in the inferior frontal gyrus
- Lateral to SLF 1 and 2; Lateral to AF



67

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#### Superior Longitudinal Fasciculus (SLF 3)

- Part of the dorsal phonological pathway in left hemisphere
   ESM = anarthria/dysarthria, phonological PE
   ESM = selective disruption of digit span performance (order rather than item errors supports phonological loop)
- May be involved in visuospatial attention, prosody and music processing in right hemisphere

Monica Ribeiro, Yordanka Nikolova Yordanova, Vincent Noblet, Guillaume Herbet, Damien Ricard, White causal and correlation evidence, Brain, Volume 147, Issue 2, February 2024, Pages 352–371

69



70



#### Arcuate Fasciculus (AF)

vAF connects mid-STG (BA 22), posterior STG (BA 22, 41, 42) and mid-MTG (BA 21) to frontoparietal operculum (pars operculum, ventral premotor cortex, sometimes pars triangularis). Passes through ventral supramarginal gyrus
 vAF connects posterior MTG and ITG to pars operculum and ventral premotor cortex and sometimes middle frontal gyrus. Passes through angular gyrus



72





## Arcuate Fasciculus (AF)

75



76

#### **Function and Clinical Correlates**

#### • Left AF

- Role in language dates back to 1800s with Broca's and Wernicke's work
- Part of the dorsal phonological stream mapping sound to articulation
- Damage associated with conduction type aphasia
  Also involved in comprehension at the word and sentence level, comprehension of sentences with complex syntactic structure and high verbal working demands calls into question clear dual stream pathway model
- Right AF
   Spatial and social cognition

#### **Function and Clinical Correlates**











82

#### Inferior Longitudinal Fasciculus (ILF)

- ILF runs through the inferior temporal gyrus and connects dorsolateral occipital cortex to the temporal pole
- Has cortical connections with the hippocampus, parahippocampal gyrus, amygdala, temporal pole, middle and inferior temporal gyrus, and extrastriate areas.





#### Inferior Longitudinal Fasciculus (ILF)



84



85

#### **Function and Clinical Correlates**

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- In the left hemisphere, part of the ventral semantic system and reading network (alexia)
- Bilaterally (right > left), involved in object and face recognition (visual agnosia, prosopagnosia), visuo-emotional integration in the cortical affective network

ulus: From Historical Reports to Ci

86

Herbet G, Zemmoura I, Duffau H. Functional Anato Hypotheses. Front Neuroanat. 2018 Sep 19;12:77









88

#### Inferior Frontal Occipital Fasciculus (IFOF)

- Fibers course from the middle occipital gyrus, inferior occipital gyrus, and precuneus passing through the superior and middle temporal gyri forming the lateral border of the temporal horn and inferior two-thirds of the atrium of the lateral ventricle
- Terminates in the OFC (BA 10 & 11) and inferior frontal regions (p0rb -BA 47 & pTri-BA 45)



#### Inferior Frontal Occipital Fasciculus (IFOF)



90

#### Inferior Frontal Occipital Fasciculus (IFOF)

Narrows into a bowtie shape at the limen insula and then extends through the anterior superior limiting sulcus of insula

Runs through the extreme capsule





# <text><image><image><image><image>





#### **Function and Clinical Correlates**

- Left IFOF part of the ventral semantic pathway
- Right IFOF involved in visual switching or rapidly shifting attention and focus between different visual stimuli and nonverbal semantic cognition
- ESM of right IFOF can disrupt face-based Theory of Mind and line bisection

97

#### **Uncinate Fasciculus (UF)**

- Connects anterior temporal pole to the frontal lobe
- Originates in the temporal pole and forms a hook shape passing through the inferior half of the anterior limiting sulcus of the insula closely paralleling the anterior IFOF
- Terminates in medial orbitofrontal cortex and dorsolateral frontal cortex





#### Uncinate Fasciculus (UF)



100

#### **Functions and Clinical Correlates**

- Thought to be involved in emotions, social emotional behavior, episodic memory
- Role in language debated based on early ESM studies but now thought to be involved in lexical semantic retrieval of more unique, proper noun categories









#### Temporo-Frontal Extreme Capsule Fasciculus

- Discovered by Petrides and Pandya (1988) in the macaque monkey
- Links the superolateral temporal lobe to the ventrolateral frontal area (BA 45 mostly)
- Courses through the extreme capsule
- Resting state fMRI connectivity between BA 45 and STS/STG and MTG
- Considered part of ventral pathway access to auditory and multisensory information via its links to the supero-lateral temporal region which, in the left hemisphere of the human brain, subserves lexico semantic processing

etrides, M. (2014). Neuroanatomy of Language Regions of the Hu nan Bri





107

#### Frontal Aslant Tract (FAT)

• FAT connects the supplementary motor complex to the inferior frontal gyrus (mainly pars operculum)



#### Frontal Aslant Tract (FAT)



109

#### **Functions and Clinical Correlates**

- Surgical injury can result in speech initiation disorders, speech hesitancy and pauses during conversations, anomia or delayed naming, errors in verb generation, perseverations
- · Deficits appear more transient than permanent in nature
- ESM of the FAT results in speech arrest or speech initiation delays
- Structural integrity correlated with verbal fluency performance
- Possible role in programming and coordination of sequential motor movements through selection among motor plans that compete for same motor resources (left specialized for speech programming, right for general action and for visuomotor integration)

La Corte et al., 2021. The frontal aslant tract: A systematic review for neurosurgical applications. Front Neurol, 12.





#### Middle Longitudinal Fasciculus (MLF)

- MLF connects angular gyrus to the temporal pole and anterior superior temporal gyrus
- Newer studies using more sophisticated imaging suggest connections between superior parietal lobe (precuneus and cuneus) to anterior STG and TP
- May be two distinct portions: AG STG/TP and SPL STG/TP









114

#### **Functions and Clinical Correlates**

- Given its connectomics, MLF may play a role in semantic processing as the AG is thought to be a higher order, heteromodal semantic hub
- ESM and resection of MLF resulted in no observable language disruption in one study

#### Vertical Occipital Fasciculus (VOF)

- Discovered by Carl Wernicke in the late  $19^{\text{th}}$  century but debated by other neuroanatomists
- Most lateral tract in the postero-lateral part of the brain running in a vertical orientation
- Ascends from the fusiform gyrus and OTS laterally to its cortical endpoints in the transverse occipital sulcus and inferior parietal sulcus and middle occipital gyrus
- Posterior to AF, lateral to ILF and IFOF

116

#### Vertical Occipital Fasciculus (VOF)





#### **Vertical Occipital Fasciculus**

- Yeatman et al performed whole brain tractography on 27 subjects identifying WMTs that consistently pass within close proximity (7 mm) of functionally defined VWFA
- 3 distinct fiber tracts identified: ILF, IFOF, VOF

Yeatman, Jason D., Andreas M. Rauschecker, and Brian A. Wa atter connections." Brain and language 125 2 (2013): 146-155...



119

#### **Vertical Occipital Fasciculus**

Damage to the VOF associated with alexia but limited to very few case reports (e.g., 50 y/o GBM with alexia w/o agraphia or hemianopsia & 40 y/o with transient alexia s/p vasc malformation resection)



Reading.—The most striking clinical abnormality in our patient was a pure alexia. She could not read despite the fact that the left calcarine cortex retained a potential connection to the list against greus. It must be concluded, therefore, that the inferior outflow of the calcarine cortex and its related vestual accipital association states are accessary coopcoments in the neural mechanisms of reading

reenblatt SH (1973) Alexia without agraphia or hemianopsia. Anatomical analysis of an autopsied case. Brain 96:307–316







#### 24 Hours PostOp



#### pig choir graduation involuntary The sun sets in the West. The capable detective discovered why 'd been waiting.

123

#### 2 Weeks Postop



pot cough prohibition unforgettable The dog sleeps on the floor. The ethical accountant understood why rd been hiding.

#### **Functions and Clinical Correlates**

- Integrates object identity with spatial location, which is important for visually guided behaviors
  Bridge between the dorsal "where" and ventral "what" stream
- Involved in reading and visual word recognition
- Damage can result in visual attention disorders and alexia

125

#### **Cingulum Bundle**

- Extends longitudinally over the corpus callosum and connects frontal, parietal and temporal lobes
- · Part of limbic circuitry



126

#### **Cingulum Bundle**

#### Subdivisions

- CB1 subrostral areas to precuneus and splenium, encircling CC
- $\bullet$  CB2 arches around splenium and extends anteriorly above CC to medial SFG
- $\bullet$  CB3 connects superior parietal lobule and precuneus with medial SFG
- CB4 minor subdivision from SPL and precuneus to frontal area
- CB5 parahippocampal cingulum fans out to occipital lobe





#### **Functions and Clinical Correlates**

- Emotion and social responsiveness, pain, motivation, executive functions (e.g, cognitive control, error detection, attentional tasks) subgenual, anterior and dorsal cingulate bundle
- Memory PHipp, retrosplenial
- Implicated in numerous clinical disorders schizophrenia, depression, PTSD, OCD, ASD, ADHD, AD
- Despite causing extensive anatomical disconnections only mild deficits (parallel pathways, distributed nature of functions)

Bubb EJ, Metzler-Baddeley C, Aggleton JP. The cingulum bundle: Anatomy, function, and dysfunction. Neurosci Biobehav Rev. 2018 Sep.92:104-127.

128















#### **Corpus Callosum**

- Primary commissural tract that connects the two hemispheres
- Four parts (A to P):
  - Rostrum fibers connect orbital frontal regions
     Genu fibers give rise to the forceps minor that connect
     frontal cortices

  - Body fibers for the corona radiata
     Splenium fibers course posteriorly and contribute to
     forceps major connecting occipital lobes



Tapetum – fibers from body and splenium that run over the lateral ventricle and connect temporal lobes

136



137

#### **Function and Clinical Correlates**

- Essential in integrating information and maintaining a unified sense of self
- Split brain studies

#### **Anterior Commissure**

- Anterior commissure connects the two hemisphere along the midline
  - Connects different parts of the limbic system and is involved in the interhemispheric transfer of visual, auditory and olfactory information between the temporal lobes
  - Composed of two fascicles<sup>1</sup> Composed of two fasculates -Anterior fascicle passes from midline anterior to the orbital frontal cortex Posterior fascicle passes from midline posterolaterally betwee the putamen and globus pallidus then dividing into temporal portion that ends in the amygdala and temporal pole and a particle locapital portion

139

#### **Posterior Commissure**

- · Posterior commissure connects the tectal areas (superior colliculi)

  - Involved in bilateral pupillary light reflex function and eye movements (vertical gaze)
     In sheep brains<sup>1</sup>, there is a fronto-temporal-occipito-pontine component that may play a role in visual information



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141

#### **Hippocampal Commissure**

Thin triangle sheet that connects the two hippocampi via fornices



142



143

#### Intersection Zones

- Temporoparietal region (IPL, pTL)
   Postop deficits aphasia, apraxia, Gerstman Syndrome, quadrantopia
   SLF, long segment of AF, MLF, ILF, IFOF, OD
  - OR





#### Intersection Zones

Frontal region

- Postop deficits contralateral weakness, apraxia, aphasia
- SLF 3, AF, CST, FAT





145

#### Intersection Zones

Postop deficits – aphasia, apraxia, Gerstman Syndrome, quadrantopia

Postop deficits – contralateral weakness, apraxia, aphasia
 SLF 3, AF, CST, FAT

Temporal Stem

Postop deficits – aphasia/semantic deficits, "pie in the sky" visual field defect, ?memory?
 ILF, IFOF, UF, Meyers Loop

146





#### **Take Home Points**

### The brain is a network, not just regions To truly appreciate the brains complexity and function, we must view it through the lens of connectomics-focusing on how different regions interact through intricate structural and functional pathways. The white matter serves as the information superhighways of the brain

- Subscription of the brain superhighways of the brain White matter is critical to brain function V hite matter is critical to brain function 0 brange to white matter disrupts network integrity, leading to diverse sensorimotor and cognitive deficits. Many neurological and poychietric disorters (e.g., MS, TBI, neurodegenerative, schizophrenia) involve white matter pathology. Ve are only beginning to understand the human connectome Advances in imaging, electrophysiology, and computational modeling are just starting to reveal the complexity of brain connectivity.
- tial for p on care
  - Understanding brain networks will be critical for targeted neuromodulation, personalized surgical planning, and predicting outcomes and recovery