Getting Started with Lesion Tracing

Introduction:
Stroke is one of the leading causes of adult disability worldwide, and despite intensive physiotherapy, up to 2/3 of stroke survivors never fully recover. There are still many unknowns about the recovery from stroke but growing areas such as neuroimaging and big data are helping to inform the field. Many neuroimaging studies are interested in understanding how different properties of lesions (e.g., their size and location in the brain) relate to various aspects of stroke recovery, such as motor recovery after stroke. However, many of the current studies rely on manually traced lesions for their analysis and therefore, the sample size of their analysis might be limited. More recently, techniques have been developed to automatically trace stroke lesions which could allow the potential of running analysis on large datasets. However, there currently are limited ways to test the accuracy of these techniques (i.e. a large set of manually traced lesions reference for comparison). Our goal is to create a large dataset of manually traced lesions in order to have a set guideline for comparing automatically traced lesions techniques and to help provide a training/test dataset for researchers who are trying to improve their automated techniques. We are hoping that this set of manually traced lesions will serve as a useful resource for researchers, providing them with manually traced lesions to assess the accuracy for their own methods. The brains that you will use to trace these lesions are from datasets collected through the ENIGMA Stroke Recovery working group. You can also read prior publications from our lab that have resulted from this manually traced dataset:

- Liew, S.-L., Zavaliangos-Petropulu, A., Jahanshad, N., Lang, C. E., Hayward, K. S., Lohse, K. R., ... & Bigjahan, B. (2020). The ENIGMA Stroke Recovery Working Group: Big data neuroimaging to study brain–behavior relationships after stroke. Human Brain Mapping.
- Liew, S.-L., Anglin, J. M., Banks, N. W., Sondag, M., Ito, K. L., Kim, H., ... & Lefebvre, S. (2018). A large, open source dataset of stroke anatomical brain images and manual lesion segmentations. Scientific data, 5, 180011. (Cited by 153 publications).
- Liew, S.L., Lo., B.P., Donnelly, M.R., Zavaliangos-Petropulu, A., Jeong, J.N., Barisano, G., … & Yu., Chunshui. (2022). A large, curated, open-source stroke neuroimaging dataset to improve lesion segmentation algorithms. Scientific data, 9, 320.

This training is composed of three sections:
1. *ITK-SNAP Tutorial*
2. *Stroke Neuroanatomy Training*
3. *Manual Segmentation Assessment*

1. ITK-SNAP Tutorial:

ITK-SNAP is the software we use for tracing. Complete the following steps to learn how to use it and practice tracing with the different included tools.

- Download ITK-SNAP here: http://www.itksnap.org/pmwiki/pmwiki.php
- Follow sections 1-4 of the ITK-SNAP User Manual: http://www.itksnap.org/docs/fullmanual.php
- Watch these YouTube videos of sample segmentations:
    - https://www.youtube.com/watch?v=ZVmINdWk5R4
    - https://www.youtube.com/watch?v=Iwmdw0XtQKk
- If you feel comfortable with using the software, move onto section 2. If you need more practice, reach out to the tracing team for further guidance.

2. Stroke Neuroanatomy Training:

To learn how to distinguish stroke lesions in the brain, which generally look like atypical structures, it is important to know what a non-lesioned brain looks like. Additionally, some pathology (WMH, PVS) in the brain may look abnormal, but is not stroke lesion. Pay close attention to these areas.

- Introduction to neuroanatomy slides: NeuroAnatomy for Lesion Tracing
- Download control subjects: /Training_Files/1_control_subjects/, open them in ITK-SNAP and practice identifying the following structures (in all three views):
    - Cortical Lobes (temporal, frontal, occipital, parietal)
    - Insula
    - Basal Ganglia (caudate, putamen, pallidum)
    - Brainstem
    - Cerebellum
    - Lateral Ventricle
    - Bonus: try to identify any WMH or PVS!

  Use the atlas resources linked at the end of this document for help!

Characteristics of…

Stroke lesions:
• Has a perilesional "halo" of medium signal-intensity around the edges, and potentially various signal intensity throughout its shape
• Asymmetrical location and shape
• Impacting nearby gyri/ventricles (appear pushed/shrunken/enlarged/etc.)

Perivascular Spaces (PVS):
• Unlikely to be seen in the brainstem/cerebellum (if it *is*, it will be very clearly following a vascular pattern)
• Generally dark/hypointense
• Very common in the basal ganglia
• Follows the vasculature of the brain
• Stringy, tube-like shape OR round/circular *(depending on which view you're in)*

White Matter Hyperintensities (WMH):
• More homogenous in signal intensity
• Generally symmetrical (occurring in the same area in both hemispheres, ie. "mirrored")
• Very common to see near the horns of the lateral ventricle horns

As you begin identifying and practicing tracing lesions, be mindful of these common tracing errors:

- *"over-tracing" or "under-tracing*": Your segmentation border should be right on the edge of where you see the lesion. With the mask at full opacity, you shouldn't see any of the lesion "peeking" out from the mask ("under-tracing"). With the mask at 20-30% opacity, you shouldn't see a brighter red mask border outlining the lesion ("over-tracing")
- *tracing non-lesioned areas*: If a lesion is near the insula, ventricles, or cortex, the lesion border can be harder to determine. In some cases, it can be helpful to trace what you think is lesion, and then go back and "erase" areas that you know are *not* lesion.
- *asymmetries*: While asymmetries are a good starting indicator that something may be a lesion, head tilt in the scanner can cause the coronal and axial views to have asymmetries that are not lesion. Be mindful of this and be sure to reference all 3 planes.

3. Manual Segmentation Assessment:

Before you start tracing lesions independently, you will first trace 5 practice subjects, receive feedback on those tracings, and then re-trace those same 5 subjects (and 2 additional new subjects). Follow these steps:

1. Download /Training_Files/1_training_lesions_set1
2. Trace lesions, following the checklist
3. Upload tracings (segmentation file) and image (T1w file) to a Google Drive folder:
    i. *"YourName_Training" -> Training_Set_1*
    ii. When you save your lesion mask, use BIDS-naming:
        sub-r001s001_desc-T1-lesion_mask.nii.gz
4. The lesion checker (Bethany/Miranda) will review your tracings and set up a meeting with you to go over everything. Make any adjustments needed to each mask, going back and forth with the checker until masks are fully approved.
5. Download /Training_Files/2_training_lesions_set2
6. Trace lesions (do not reference the past tracings)
7. Upload to Google Drive, meet with the checker until tracings are fully approved

After completing both sets of tracings and checker has fully approved, you are a fully trained lesion tracer and ready to start independently working on data!

Keeping Notes

Throughout your training and when you begin independently tracing lesions, it will be vital that you keep detailed notes in your notes document, titled *YourName_Training_Notes*.

This is especially important for any trouble images that you may come across. Examples of trouble lesions might be if there were multiple lesions in the brain, odd lesions that you may be unsure about the accuracy of many small white matter lesions, etc. You can refer to your notes when you discuss with your team and this can be referred to during quality checking.

Using a Tablet

It can be useful to trace lesions using an electronic pen and tablet. There are several Wacom tablets located in the lab that can be used and checked out. Alternatively, if you have a tablet (Microsoft Surface, iPad, etc.) you may prefer tracing with a stylus/pen. Others prefer using a normal mouse or trackpad. See what works for you.

Tracing Checklist Steps:

1. Find the T1 nifti file in the finder > right-click "open with" > ITK-SNAP > "Load as Main Image" **DO NOT DOUBLE CLICK FILE
    To Load a Mask:
    1. *Open the T1 (same instructions as above)*
    2. *Open the mask file (click "Load as Segmentation")*
2. **Locate lesion** (easier said than done in some cases. If there are multiple lesions, trace all and include in the same mask)
    a. In the axial (or coronal) view, start posteriorly and scroll through the cerebellum
    b. Then scroll through and focus on the brainstem
    c. Then scroll through and focus on the left hemisphere
    d. Then scroll through and focus on the right hemisphere
3. **Begin tracing lesion**

a. May be easiest to start in the center of the lesion (however this based on preference)
b. Use one plane/view to start. Choose the plane/view where you see the lesion most clearly. Even if you are tracing in one view, check the other views frequently to see if what you are tracing looks like lesion in those views as well.
c. Select polygon mode and 'smooth curve' option
d. Outline the lesion by clicking or dragging around the borders of the lesion
e. Once an outline is made, click complete, then accept if there are no further changes to make; you should now see a filled slice
f. For medium to large lesions, trace in *either* coronal or axial view, and then go and clean up the borders (if needed) in the *other* view
g. For large lesions, the 'interpolate' tool can be used:
    i. Trace every 2 or 3 slices, repeating until slices have been traced throughout the entirety of the lesion
    ii. Go to Tools > Interpolate Labels (only click ONCE)

4. **When finished tracing, review:**
    a. Turn the mask opacity down to about 20%, and look for any additional lesions
    b. Scroll through in both the coronal and axial views, watching the borders of the mask. Note where there might be any large "jumps" or very straight edges, and fix if needed
    c. Don't trace *any* of the insula
    d. Don't trace *any* of the ventricles
    e. Don't trace *any* of the dura mater (white border on the skull)

If you are having trouble determining the lesion border:

1. Use the crosshairs and click on the border you're unsure about, then look in the other views and scroll through to see if that area is "connected" to anything
2. Look at the general shape and "movement" of the lesion

HELPFUL LINKS:

itk-SNAP Shortcuts:
http://www.itksnap.org/pmwiki/pmwiki.php?n=Documentation.KeyboardShortcuts

S = show or hide the segmentation
Shift+**X** = show or hide crosshairs
Hold Right-Click + Drag = zoom in and out

Neuroanatomy Atlases:
https://neurology.mhmedical.com/book.aspx?bookID=1854#129941473
https://www.imaios.com/en/e-anatomy/brain/mri-axial-brain
https://radiopaedia.org/cases/brain-lobes-annotated-mri-1