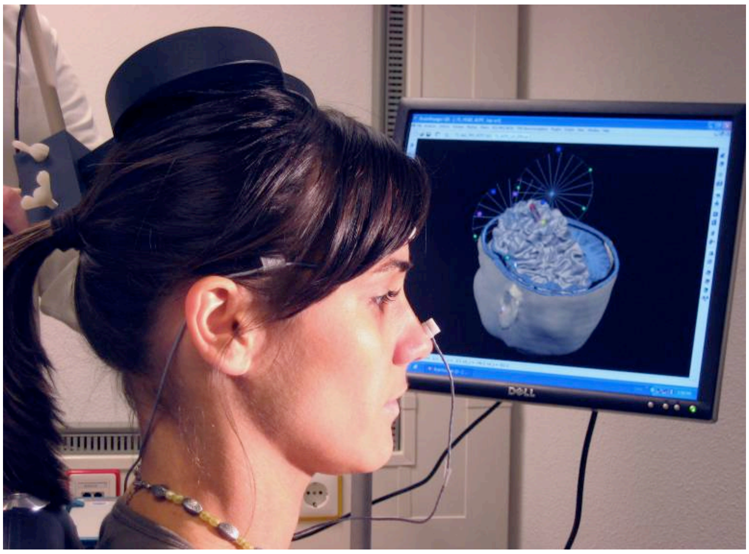
BRAINVOYAGER ™

TMS NEURONAVIGATOR



User Manual

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Preface

Welcome to the BrainVoyager TMS Neuronavigator. Transcranial Magnetic Stimulation (TMS) is by now a well-established tool for inducing transient changes in brain activity non-invasively in conscious human volunteers. The BrainVoyager TMS Neuronavigator enables a precise and individual navigation of a TMS coil above a specific anatomical area of the brain, as well as an imaging-guided navigation of the TMS coil to functionally defined brain regions-of-interest.

An increasing amount of studies have used the behaviour-modulating capacity of TMS to reveal causal brain-behaviour relationships, investigating a continuously increasing range of different behavioural, cognitive, and affective functions. Recently, TMS has also been applied as therapeutic tool for treating a variety of neurological and psychiatric disorders including, e.g., depression, neglect, stroke, or schizophrenia.

All these studies clearly demonstrate the potential of TMS to serve as unique research tool for the investigation of a broad variety of issues in cognitive neuroscience. Different experimental TMS protocols can be designed to address questions concerning the location, timing, lateralization, functional relevance or plasticity of the neuronal correlates of information processing. The hypotheses underlying these different experimental TMS protocols can be based on respective results of functional imaging studies, neuropsychology, or animal models, investigating the same paradigms and neuronal pathways from methodologically different perspectives.

The increasing use of TMS in cognitive neuroscience and neuropsychiatry requires a precise positioning of the TMS coil above a specific anatomically or functionally defined brain region. They have to be ascertained individually for every subject, respectively patient. Only such an individual imaging-guided Neuronavigation of the TMS coil is capable of achieving the precision in positioning the TMS coil, necessary for successful and reliable TMS experiments and clinical treatments. Moreover, only TMS Neuronavigation explicitly accounts for the inter-individual differences in brain anatomy as well as for the inter-individual differences in the functional architecture of the brain when applying TMS both in cognitive neuroscience and clinical therapy.

TMS neuronavigation technique

During TMS neuronavigation, stereotactical data for the localization of the TMS stimulation site are recorded in real-time using an ultrasound-based position measurement system (CMS20/TMS). This system consists of several miniature ultrasound senders, which are attached to the participant's head as well as to the TMS coil and digitizer pen. These ultrasound senders continuously transmit ultrasonic pulses to a receiving sensor device. The measurement of the relative spatial position of these senders in 3d space is based on the travel time of the transmitted ultrasonic pulses to the three microphones built into the T-shaped measurement device. In the next step, local spatial coordinate systems are created by linking the "real world" spatial position of the ultrasonic senders to a set of fixed additional landmarks on the participant's head. The specification of these fixed landmarks is achieved by using a digitizing pen that also hosts two transmitting ultrasonic senders in order to measure its relative position in 3d space. The nasion and the two pre-auricular points (at the incisions of the auricles) are used as important anatomical landmarks in order to define the real world central coordinate system. After this stage, the system provides topographic information of the head's ultrasonic senders relative to a participant-centred coordinate frame. Similarly, the TMS coil also hosts a set of ultrasonic senders, whose relative spatial positions are linked to fixed landmarks specified on the coil in order to calculate another coil-specific coordinate system. Once the 2 local spatial coordinate systems are defined for the participant's head and the TMS coil, they have to be coregistered with the coordinate system of the MR-display space in BrainVoyager QX. The same anatomical landmarks are identified in the MRI scan display as on the real participant's head and coregistered with the coordinates measured with the digitizer.

After assigning the landmarks on the real subject's head and coregistration with those on the transparently formed head model with the underlying cortex reconstruction or sliceable volumetric anatomical displays of brain structures, the movements of the TMS coil over the surface of the subject's head are registered in real-time. In addition, the coil is visualized as 3d model pointing with a defined assumed signal distribution beam to the individual brain reconstructions and calculates the distance of the current coil/ central beam position to a defined target point, where you can fixate the coil and stimulate the area. The distances are displayed continuously. The coordinates of target points can be stored/ predefined.

By superimposing functional data on the anatomical reconstruction of the brain hemispheres, the TMS coil can be neuronavigated to a specific anatomical and/or functional activation area of every participant. TMS neuronavigation should always be based on data in AC-PC space (rotating the cerebrum into the anterior commissure – posterior commissure plane) in order to avoid any additional transformations that could distort the correspondence between MRI and stereotactical points.

STEP 1: SETUP

1.1 CMS20 Parts and Setup Instructions

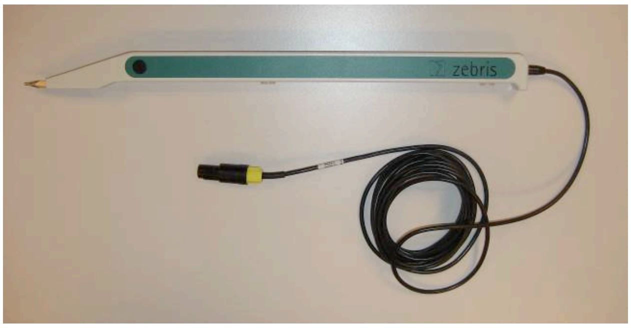
The CMS20 system consists of:

- The main unit: Model I or the new extended Model II (Picture A)
- A power supply adapter with plugs (Picture B)
- A cable to connect the main unit with your PC / Notebook (Picture C)
- A measuring device receiving the ultrasound signals (Picture D)
- A digitizing pen (Picture E)
- Three single senders to be attached to the participant’s head (Picture F)
- a triple-sender + holding device to be attached to the TMS coil (Picture G/H)
- Stickers to attach the 3 single senders to the participant’s head (Picture I)
- BrainVoyager QX for TMS software and CMS20 driver software

Picture A **Model I** **Model II**

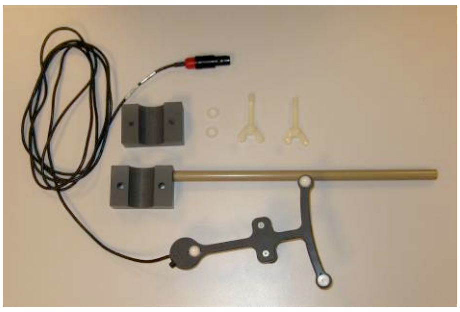
Picture B

Picture C



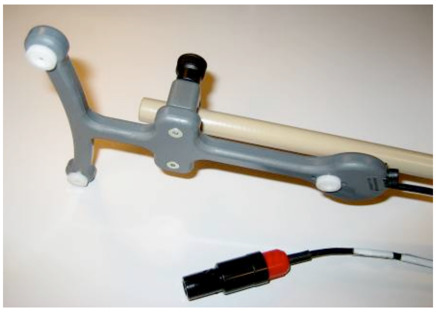
Picture D

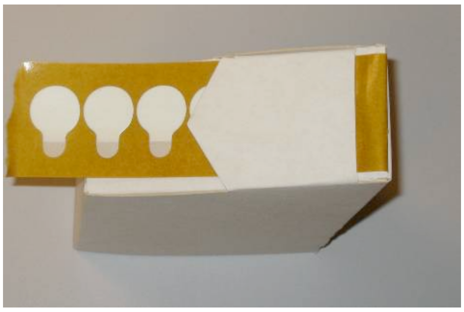
Picture E



Picture F

Picture G





Picture H

Picture I

Setup Instructions

1. Connect the main unit (A) via the power supply cable (B) to an outlet.
2. Connect the main unit (A) via the USB connection cable (C) to your PC.
3. Plug the measuring device (D) into the main unit (A)
   Note: color of plug and input should match: grey to grey
4. Plug the digitizing pen (E) into the main unit (A)
   Note: color of plug and input should match: yellow to yellow
5. Plug the 3 free senders (F) into the main unit (A)
   Note: color of plug and input should match: blue to blue
6. Plug the triple-senders (G/H) into the main unit (A)
   Note: color of plug and input should match: red to red

Software installation

Concerning the software installation of **BrainVoyager QX_TMS** for Windows OS follow the instructions "**BrainVoyager QX – Installation with HASP key**". Built up the CMS20 hardware following the instructions above and install the **CMS20/ Zebris driver** zebris_drivers_usb.exe you find on the CD or on your computer at

/Program Files/BrainVoyager QX/ZEBRIS_TMS/ZebrisUSBDriver/

If you attach your computer via the USB cable to the main CMS20 unit and activate it (turn on power/ connect power cables) Windows will detect the system as new hardware and asks for the driver setup. Browse the driver setup zebris_drivers_usb.exe on the CD or the local program directory and follow the Windows installer instructions. Note the driver will also make a user directory for temporary files during the measurement. If you use different User Logins, it is the best you install the driver again to create this working directory in the BVQXExtensions folder for the current in-logged user.

Remark: BVQXSampleData and BVQXExtensions directories are user specific. You need to copy them with their content (e.g. scripts, Plugin programs) for every user, who is working with individual login and in secured user partitions.

1.2 Quick System Test

For a quick system test we have prepared MRI/FMRI sample data in BrainVoyager QX. You can find those data on the BrainVoyager QX TMS setup CD. Copy and unpack the *.ZIP into the <USER>/BVQXSampleData directory.

First we need to load all necessary MRI files for navigation into BrainVoyager QX. In addition we need a test person (or a physical head model), measure and coregister his/her/the head and a TMS coil to run the navigation at the end. A TMS application is not necessary for the navigation system test.

After setting up the CMS20 hardware like described before, start BrainVoyager QX with the HASP attached. Via File/Open load the **CG_ACPC.VMR**. Open the Surface Module by clicking the Surf button in the Volume Tool menu. Load the **CG_ACPC_HEAD.SRF** via the Meshes menu you find at the header bar of the program. Cut the head mesh by clicking the 5th button from top on the right Surface function menu bar of the program.

Remark: A short guide for essential Surface Module functions and navigation can be studied in the table on page 13. Learn to move and turn the meshes.

Analogue to the result in Step 4 (page 33), load the **CG_ACPC.FDP** head marker points of the head model at the TMS Neuronavigation menu/ Set Head Mesh Fiducials … dialogue. Switch to Mesh Menu/ Add Mesh and add the brain reconstruction **CG_ACPC_MERGED8K.SRF - a** merged simplified head reconstruction model of two segmented brain hemispheres.

Open via Scene menu at the header bar Scene overview. With changing the check mark here you can select the surface you like to operate on. Select the merged cortex mesh **CG_ACPC_MERGED8K** as “Current”.

Open the TMS Neuronavigation/Navigation menu and select a **navigation target point** (fiducial) on the brain surface by CTRL+left mouse click. You can also save its coordinates in a text file as *.TGP to remember the position and if you plan to stimulate more than one position or one repeatedly in different sessions then you can load that target again.

Switch the check mark in Scene overview to the **Head mesh** and click the 5th button from top of the right Surface Module functions bar to close the head mesh and the 5th button from below allowing you to look through the skull on the cortical surface with the navigation target you plan to hit with the virtual beam of the coil model. The display size and radius of the coil beam can be modeled in the Navigation menu - coil settings tab (see STEP 3, p. 31).

Continue in the TMS Neuronavigation menu. Following STEP 5 (p. 35-38), measure and coregister the participant's head. The WHITE FDP marker fiducials of the head model should fall almost on the measured RED head point fiducials (nasion, left and right ear points) of the participant if his head properties are not too different from the used head model. However for general testing this precision is sufficient. Then continue with STEP 6 (p. 39), measure and coregister your TMS coil.

After making the TMS coil transparent (wire frame display, p. 42) and modeling the beam, place the TMS coil on the head of your subject and move it towards the target point by simultaneously controlling your actions at the computer display. The red numbers on the display will turn into yellow and green when you get closer to the target or hit it at 0. Now you can fixate the coil and apply the TMS stimulation to the selected brain area.

The coil movements on the display should follow your navigation actions on the subject's head if the coregistration steps are done as described and the CMS20 hardware was setup correctly and working fine.

1.3 Arrangement

The participant / patient should always face the measuring device (D) in a distance of approximately 1.5 - 2 meters. The whole setup should ensure that all eight senders (three on the participant's head, triple-sender on the TMS coil and the two senders of the digitizing pen) are facing the measuring device (D). No obstacle should be placed in between in order to ensure that the measuring device receives all ultrasound signals. The T-shape measurement device with the 3 microphones can be tilted a bit forward but not 90 degrees or more to the left or right (as on the font picture). That can cause navigation errors of the coil (based on errors in coregistration). Imagine the 3 senders in the face of the subject and those of the triple marker on the coil have a triangle configuration corresponding with the triangle configuration of the microphones on the measurement device. The BrainVoyager QX software should be installed on a PC or notebook ideally located next to or behind the participant in order to allow a real-time TMS neuronavigation by the researcher.

Reasons for coregistration errors and malfunctions in navigation:

- **Application errors:** forgotten coregister button press; "long" button press on digitizer pen; not deleted corrections of selected coregistration points (Press the digitizer button when you are sure to have identified the right point on the subjects head. Avoid insecure actions! If something went wrong, better restart the program, load the files from the Recent File and Mesh menu and start again the coregistration in the TMS Neuronavigation dialogue). After pressing the coregister button corrections are not possible while the system is running.
- **Setup conditions:** higher distance, electromagnetic sources, reflecting environment, position of microphones relative to coil senders/ wrong configuration or selection order of head senders/ head points; obstacles between senders and microphones;
- **Defects of device components:** broken cables, senders - check recording entries!);

Navigation in the BrainVoyager QX Surface Module

The following functions you should learn for mesh manipulations on the display:

Closed surface display (e.g. brain hemisphere)	**Shaded mesh button** active	On the right 11th button of the surface control panel
Transparent surface display (e.g. head)	**Wire-frame button** active	On the right 12th button of the surface control panel
Surface Navigation Mode	**Navigation mode button** active	On the right 3rd button of the surface control panel
Turning the surface in **3d** space	Keep the **left mouse button** pressed down and move towards left and right or back and forth	Mouse or touch pad control
Moving the head in **2d** space left and right or up and down or diagonal	Keep the **left mouse button** pressed down and press the **Shift button** and move the mouse towards left and right or back and forth	Mouse or touch pad control + Keyboard
Zooming in and out of the scene or increasing and decreasing of the surface display	Keep the **left mouse button** pressed down and press the **SHIFT** + **CRTL** button and move the mouse back and forth	Mouse or touch pad control + Keyboard
Slicing mode	Cutting + slicing buttons active	On the right of the surface control panel: 3 pairs of buttons
Cutting the head horizontally	TRA cutting + TRA slicing buttons.active	Transversal buttons
Cutting the head sagittal	SAG cutting + SAG slicing buttons.active	Sagittal buttons
Cutting the head left – right	COR cutting + COR slicing buttons.active	Coronal buttons
Moving the **cutting plane**	Left mouse button down + ALT button + moving back and forth or left and right	Mouse or touch pad control + Keyboard
Mesh selection if you have loaded more than 1 mesh	Select the mesh you like to change, e.g. transparency or color	At Scene menu, Scene overview tab

STEP 2: Preparing MRI data for TMS neuronavigation

TMS neuronavigation requires at least one set of individual high resolution (1x1x1 mm3) structural MRI data of the head and brain of your subject (preferred measured in sagittal slices) and optional also functional MRI data coregistered with the structural data set. Other options like navigation based on normalized data (e.g. Talairach coordinates, Brodman area atlas “estimates”) or outer landmarks on the head of your subject (like used for the positioning of EEG electrodes) don’t offer a precise localization of individual brain areas. You might be able to hit certain areas depending on the extension of the magnetic field of your TMS coil (a circular coil is not focussed like a figure eight coil) and the local variability of certain brain areas. However, you will not be sure what is below the head surface when you have no individual data. This is valid for anatomical brain areas as well as for functional brain areas.

2.1 Magnetic Resonance Imaging - Data acquisition

Essential: T1 weighted 3D structural MRI data - sagittal slices covering the whole head respectable the brain of the subject, if possible 1x1x1 mm3, with certain homogeneity (minimal like sample data CG2_3DT1FL_CLEAN.vmr of the Getting Started Guide) to allow automatic segmentation of the cortical surface afterwards. When you fixate the head of the subject avoid placing the cushions to tight on the ears if you like to use the ear points for coregistration.

Optional: Several 3D T1 weighted data sets of the same subject for VMR-averaging to increase homogeneity for automatic segmentation.

Optional: T2 weighted EPI functional MRI data – related to the paradigm you like to study the subject with TMS combined with psychophysical tests (behavioural measures) after the MRI investigation, e.g. to understand the temporal order or timing of cognitive processes, contribution of brain areas in the processing of a certain task.

2.2 MRI data analysis and visualizations in BrainVoyager QX

To use the BrainVoyager TMS Neuronavigator, our collected MRI data need to be analyzed and visualized in BrainVoyager QX to receive a computerized head and brain model as navigation reference where you can remove the scull, slice the head containing the brain structures or to make the head surface transparent seeing the underlying modelled cortex. Although the basic steps for preparing the required files are described below, please also consult the BrainVoyager QX Getting Started Guide for more functional details of the BrainVoyager software and explanations how to analyze and visualize anatomical and functional projects.

Required:

- 3D anatomical project (VMR File in AC-PC plane) (see 2.2.1 and 2.2.2)
- Surface reconstruction of the head (SRF File) (see 2.2)
- Segmentation and reconstruction of cortical surfaces (2 SRF Files or 1 merged SRF) (see 2.2)

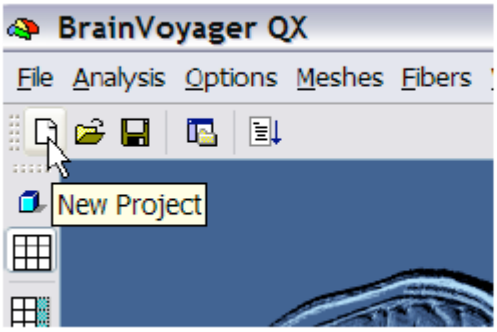
Optional:

- Functional activation map (GLM and / or VMP / SMP File) – see Getting Started Guide

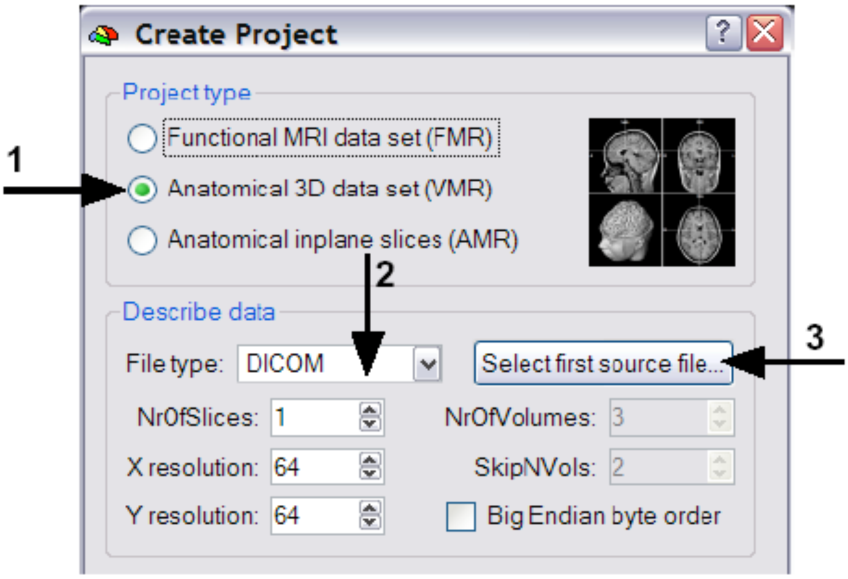
2.2.1 Creation of a 3D anatomical project (VMR File)

In this step we will learn how to create 3d anatomical projects (VMR Files). For details please also consult the BrainVoyager QX Getting Started Guide!

1. Click on the "New Project icon" to open the "Create Project" dialog.



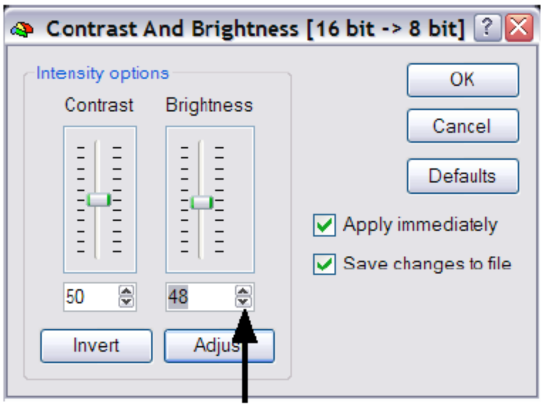
In the "Project Type" section, check "Anatomical 3D data set (VMR)".



2. In the "Describe data" section, select your file type (e.g. DICOM, or GE_MR, or…).

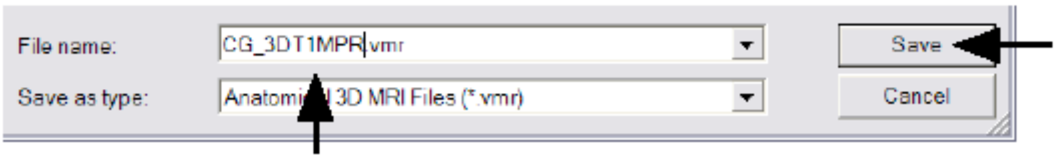
3. Click the "Select first source file..." button and navigate to the folder containing your brain imaging data. Select the first file of your anatomical measurement and click “Open”. In the “Number of Slices” edit box, enter the number of slices of your 3D data set.

Click the “GO” button to build the VMR project.



The assembled images appear in the workspace and the “Contrast and Brightness [16 bit -> 8bit]” dialog appears. In this dialog you can change the brightness and contrast.

Click the “OK” button to close this dialog.



After closing the “Contrast and Brightness [16 bit -> 8bit]” dialog, use the menu item “File” -> “Save as” to save the project. A “Save as...” dialog will appear and you can save the VMR project using, e.g., the initials of your participant.

Remark: Following the Getting Started Guide the beginner can also use the *Project Wizard* assisting you to select the right files.

You can explore this 3d data set by clicking the left mouse button at any point within the “SAG”, “COR” and “TRA” view. This will define the “current” voxel, which is highlighted by the white cross. The three views are automatically updated to show a sagittal, axial and coronal slice running through the specified 3d point. You can also change the position of the white cross by holding down the left mouse button while moving the mouse. Notice that the intensity value and current position of the mouse cursor is shown in the “Info” tab of the side bar, even without clicking in the dataset.

4. Cleaning for Head mesh reconstruction: Open the 3D Volume Tools Dialog – Full Dialog -> Segmentation Tab. In the Value Range group, specify the lower threshold by changing the value Min to 35 and click the Grow region button. You will see that all voxels within the specified range are coloured blue. If there are some voxels of the head/ brain are still grey lower the value and press the Expand button. Press the Reload Marked button and save the data set as *CLEAN.VMR.

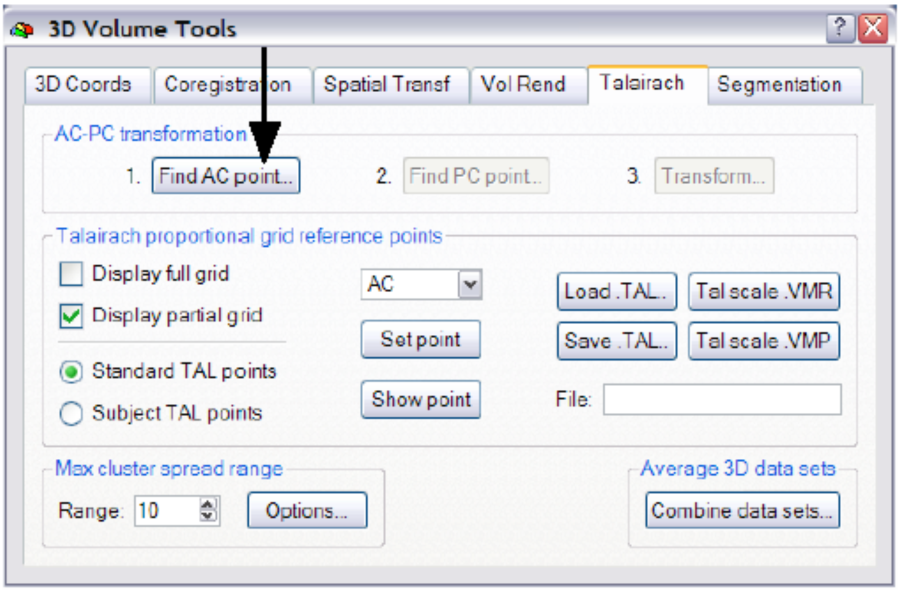
Remark: In the case of errors press Reload All button. You can check the back ground values when you move the mouse cursor through the 3D views outside of the head/brain data. [The 3 info/file panes must be closed.] You see the x,y,z coordinates of voxel and intensity values on the lower menu bar.

2.2.2 Transforming anatomical data into the AC-PC plane

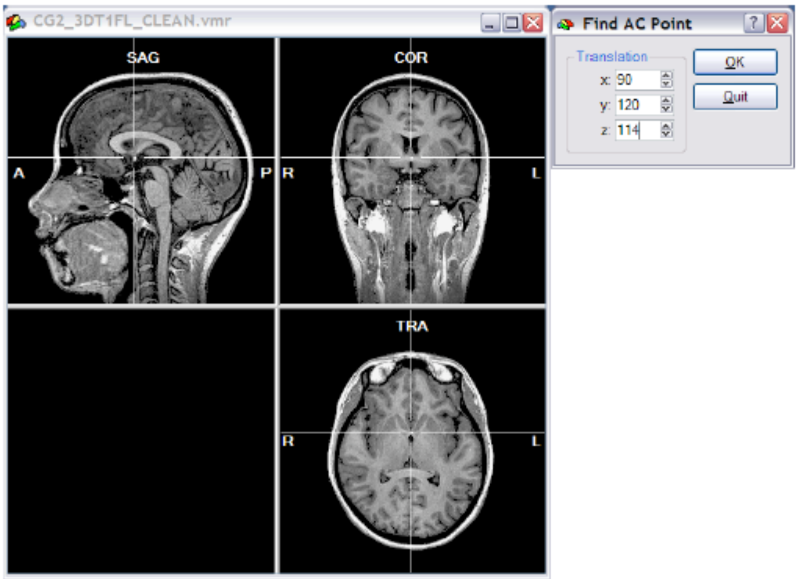
Click the “Open” icon or select the “File -> Open” menu item and open the cleaned VMR file as created under point 2.1.1.

In the next step we will translate and rotate the cerebrum into the AC-PC plane (AC = anterior commissure, PC = posterior commissure). This step is performed in the “Talairach” tab of the “3D Volume Tools” dialog.

Switch to the “Talairach” tab of the “3D Volume Tools” dialog.



1. Click the “Find AC point…” button in the “Talairach” tab of the “3D Volume Tools” dialog. The 3D Volume Tools” dialog will be replaced by the “Find AC Point” dialog.

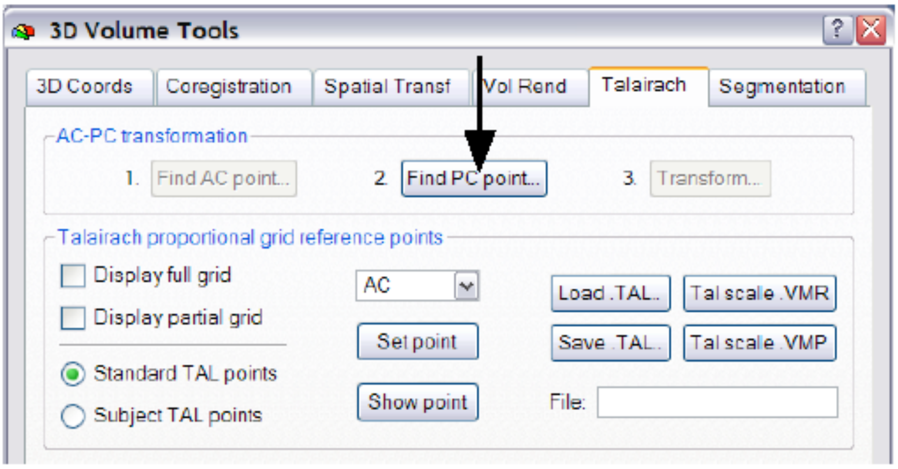


You can directly move the cross by clicking the spin controls of the “Find AC point” dialog. The most convenient but still precise navigation method is using the cursor keys, try the left, right, up and down cursor key as well as SHIFT-UP and SHIFT-DOWN (for details, see the “keyboard and mouse functions” in the User’s Guide).

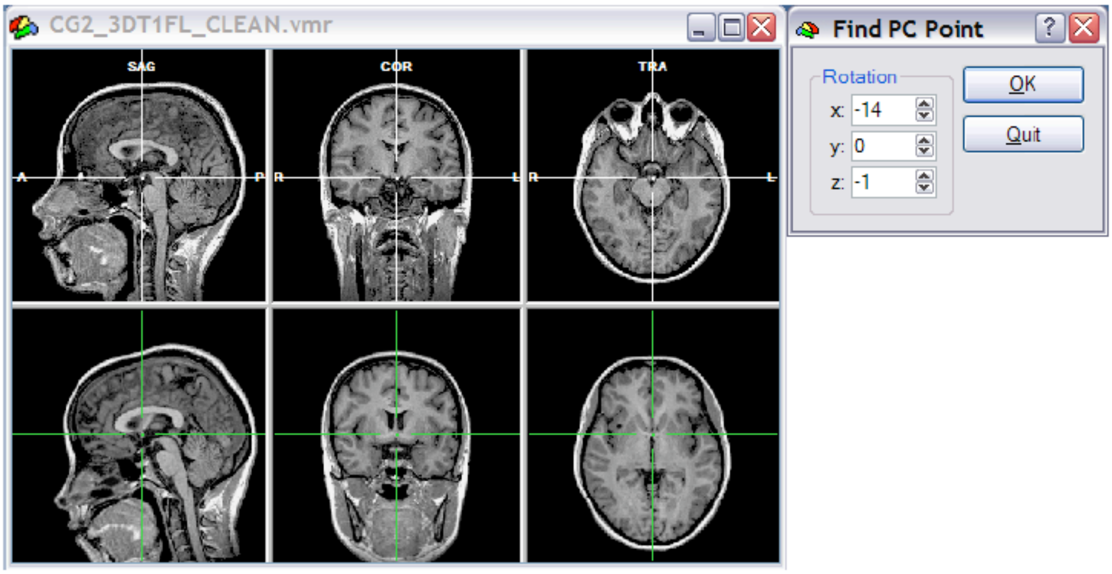
2. Now click the "OK" button in the "Find AC Point" dialog. The dialog will be replaced by the "3D Volume Tools" dialog and appropriate translation parameters (in the x, y, and z direction) will be specified for the AC-PC transformation. The display now also changes into the 2 x 3 arrangement. The upper row displays the original data set while the lower row shows the data set after application of the specified transformation.

Tip: It might be helpful to zoom the view by clicking the "Zoom In" icon. Another possibility is to use CTRL-T, which cycles through an enlarged view of the "SAG", "COR", "TRA" and the standard view.

3. After having specified the AC point, the "Find AC point…" button is disabled and the "Find PC point…" button is enabled in the "Talairach" tab of the "3D Volume Tools". The next task is to rotate the data set in the coregistration window (lower row) in such a way that we also see the posterior commissure in the axial slice. To find the posterior commissure, click the "Find PC point…" button. The "Find PC Point" dialog will appear on the right side of the "VMR" window.



Use the "x" spin control in the "Rotation" field to rotate the dataset in the lower row until the view shows the posterior commissure. The rotation is executed around the position of the green cross. Since the cross is located at the anterior commissure, it will remain visible in the coregistration window despite rotation.

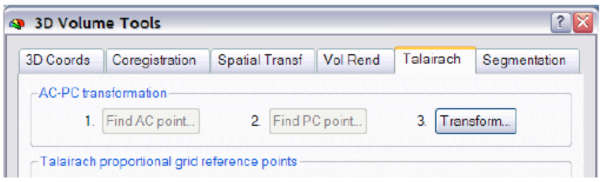


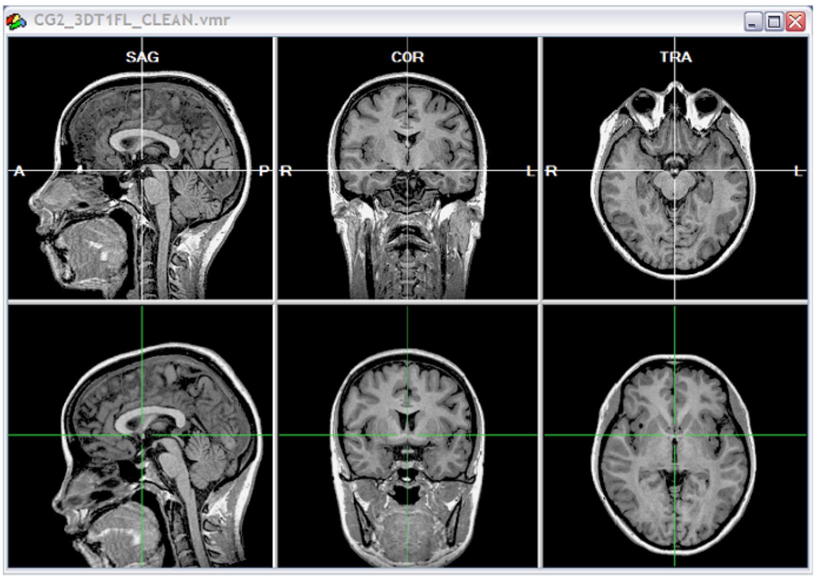
The green cross can be used to adjust two additional angles, if necessary. Change the "z" angle to rotate the dataset in the coregistration window so that the green cross runs through the middle of the brain hemispheres. Now click the "OK" button in the "Find PC Point" dialog.

Tip: It might be helpful to hide the green and white cross temporarily. Deselect the “Show cross” item in the “3D Coords” tab. More conveniently, you can also press the “A” key to display or hide the green / white cross.

Info: The “Find AC Point” and “Find PC Point” dialogs provide a convenient way to specify the AC-PC transformation values. You can do the same steps also directly in the “Co-registration” tab. After you have placed the green cross on the AC, click the “Set Translation” button to fixate this point. If you click in the dataset afterwards, you can get back to the AC by clicking the “Center” button. Then adjust the rotation parameters by using the spin controls in the “Rotation” field on the “Coregistration” tab.

4. After having specified also the PC point, the “Find PC point…” button is disabled and the “Transform…” button in the “AC-PC” transformation field of the “Talairach” tab is enabled. In order to save the specified transformation (translation and rotation values) and to apply them to the 3D data set, click the “Transform…” button.





5. After clicking the "Transform…" button an "Export VMR" dialog for saving the transformation values opens automatically. BrainVoyager QX will suggest the filename: "Name of raw VMR"_ACPC for both the .TRF as the .VMR file. After the selection of points we need to apply a rigid body transformation to the 3D data set. Select the SINC interpolation option. That will keep structural properties required for automatic segmentation. Finally click the "GO" button.

The specified spatial transformation is now applied to the data set. After a few seconds the resulting new 3D volume has been computed and saved to disk. In addition, it is also shown automatically in a new "3D Volume" window. The centre of the new data set is now the AC point and the brain is located in the AC-PC plane. This can be seen clearly in the "TRA" view, which shows both AC and PC. Close the other .VMR.

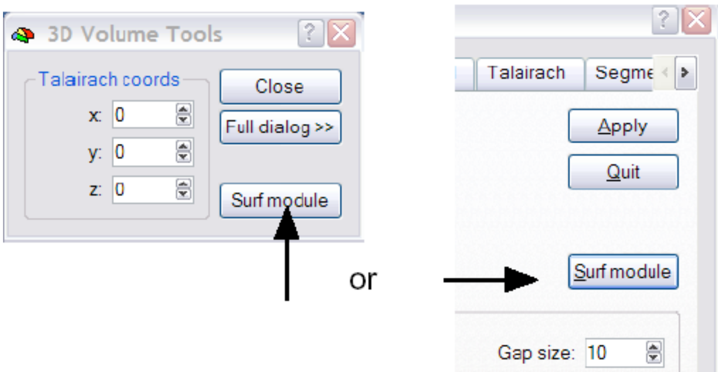
This volume data set in subject's individual AC-PC space will be the basis for TMS Neuronavigation. However, we will not use directly the volume data but surface reconstructions of head and cortex allowing us faster navigation than possible on volume renderings.

The following chapter will demonstrate how to segment the head and brain and reconstruct the surface of head and brain hemispheres.

2.2.3 Surface reconstruction of the head and cortex

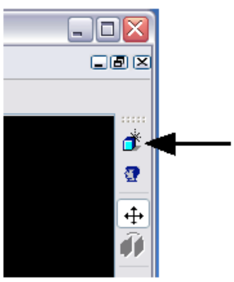
Now we will learn how to create a 3d model of a participant's head from a 3d MRI data set. The resulting visualizations are important for the spatial coregistration of a participant's MRI 3d coordinate system with the real-world space measured with the CMS20 position measurement device to allow TMS-Neuronavigation.

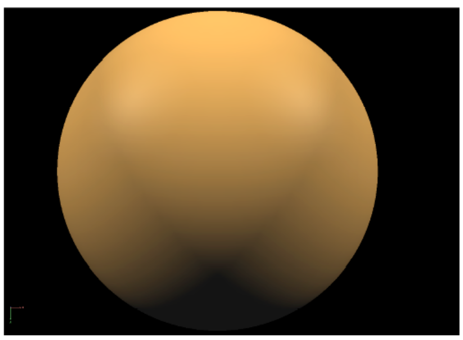
1. Open the cleaned VMR in AC-PC space as prepared in 2.2.1 and 2.2.2.



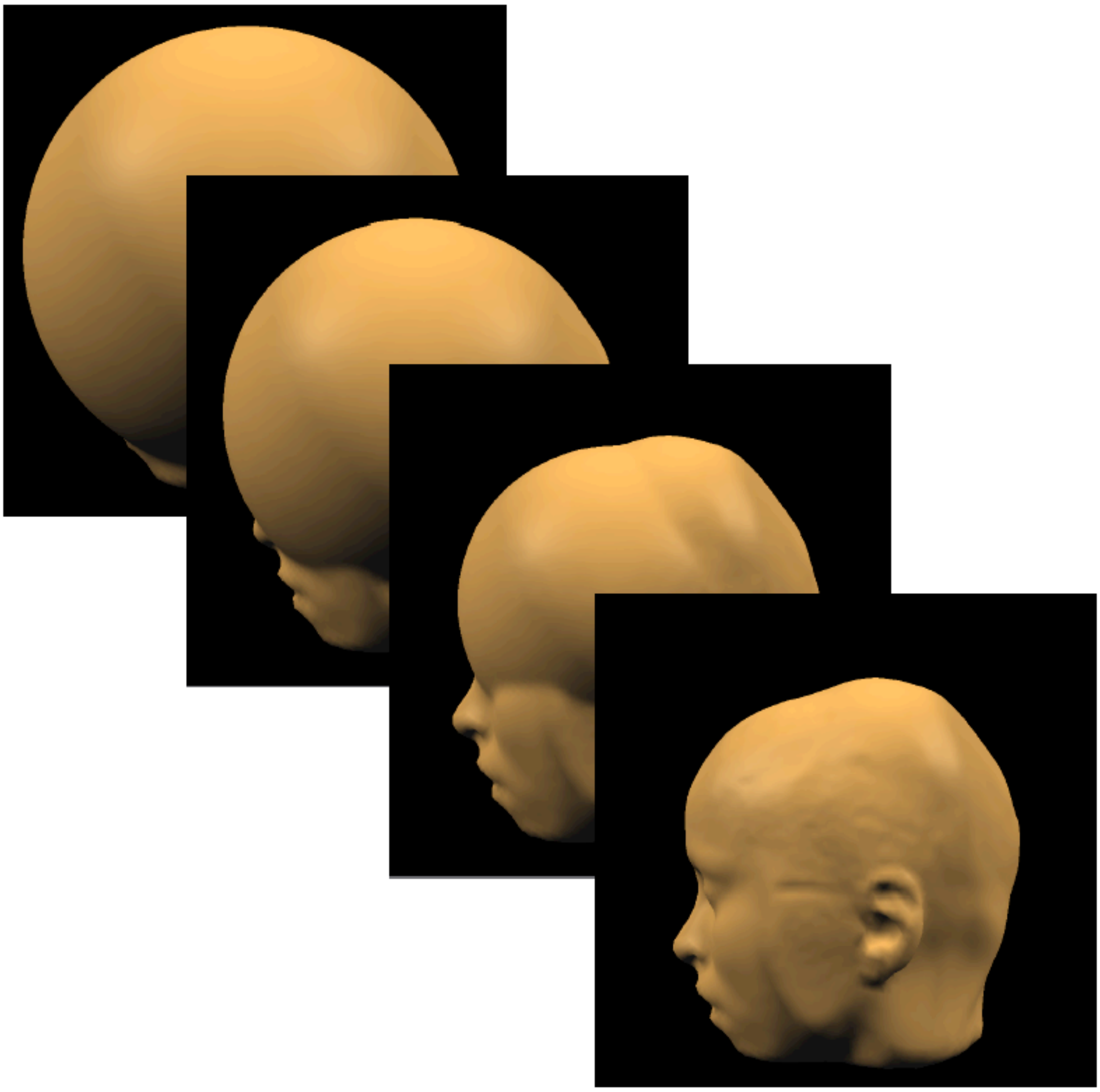
2. In the "3D Volume Tools" dialog, click on "Surf module" when the dialog is till in mini-state. If the "3D Volume Tools" is in full dialog state select the "3D Coords" tab and click the "Surf module" button.

3. Click the "Create mesh" icon in the "Mesh Tool Box". The surface module window will show a sphere, which is the mesh created as default.

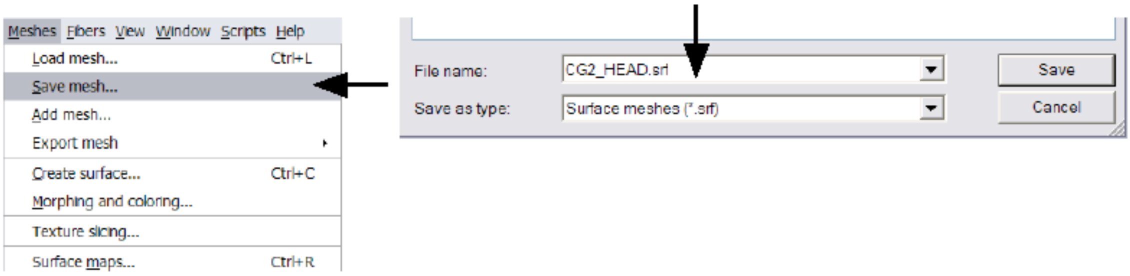




4. Click the "Morph mesh" icon to start a "shrink-wrap" reconstruction procedure. The invoked process reduces the radius of the sphere until the vertices of the mesh "detect" tissue, which corresponds in our case to the skin of the participant's head. The procedure iterates until the complete head is reconstructed as shown below.



5. We now save the created polygon mesh. Click the “Meshes-> Save mesh...” menu item. In the appearing “Save As” dialog, enter <Subject Initials>_HEAD.SRF and click the “Save” button.



At this point, we have successfully prepared 1.) a VMR file in AC-PC (3d anatomical data set), and 2.) a surface reconstruction of the participant’s head. These files are sufficient to use the BrainVoyager TMS Neuronavigator.

However, it might be beneficial to also prepare a segmented reconstruction of the cortical surface of one or both hemispheres. This allows a more precise TMS Neuronavigation to a particular anatomical region of the cortex.

6. For an automatic segmentation of the brain hemisphere in BrainVoyager QX we need specifications of Talairach points in the ACPC.VMR. Because we plan to use a prepared Talairach mask file to identify midbrain structures, ventricles, and the cerebellum, structures we can exclude automatically before cortex reconstruction.

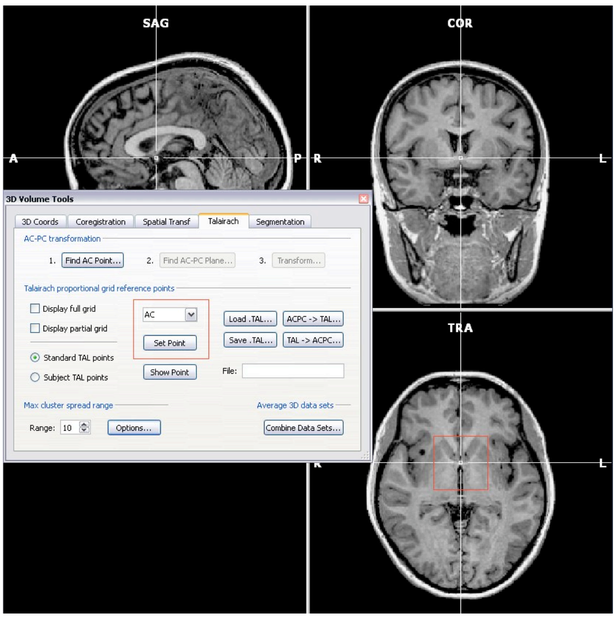
Remarks: The saved individual Talairach transformation parameters and the normalized anatomical volume data (TAL.VMR) could be used for other purpose (e.g. in combination with functional MRI data).

Considering the requirement to publish your fMRI data in a normalized brain atlas, often naïve users are asking if we can stimulate the individual brain based on normalized data or not. Technically the question seems to be obvious and we could save resources for individual functional MRI measurements using a functional brain atlas. However, the success to hit the individual area depends on the local and probably also functional variation of individual brains and the distribution of the magnetic field of the TMS coil. (The latter might be physically defined but the distribution through the different tissues stays unclear/ not measurable.)

Technically it is possible in BrainVoyager QX for specific cases: The key function is the “Volume of Interest” VOI file you can generate at “Volume of Interest Analysis” tool based on functional data/ maps. You can back-transform the TAL VOI of functional volume data (TAL.VTC) into individual ACPC space. In that VOI you can place the navigation target point.

However, a direct calculation function, where you enter arbitrary TAL coordinates from a text book, cannot be back transformed in ACPC space with the current BrainVoyager QX volume tools. It is planned for one of the next updates. If this method would make sense for individual TMS needs to be evaluated by the user. There is a study by two of the authors comparing 3 methods and their effect strength in TMS application for a particular brain area involving Talairach coordinates (see: A. Sack et al. (2009). *Optimizing functional accuracy of TMS in cognitive studies: A comparison of methods.* **Journal of Cognitive Neuroscience**, 21.2.).

Go to Talairach tab in the 3D Volume Tools Dialog. The white cross should be at AC when you have loaded the ACPC.vmr file and clicked Show Point. At Talairch proportional grid reference points AC should be selected – click Set Point button, browse to PC – the cross will jump towards PC – with Shift+Cursor down place the cross above the posterior

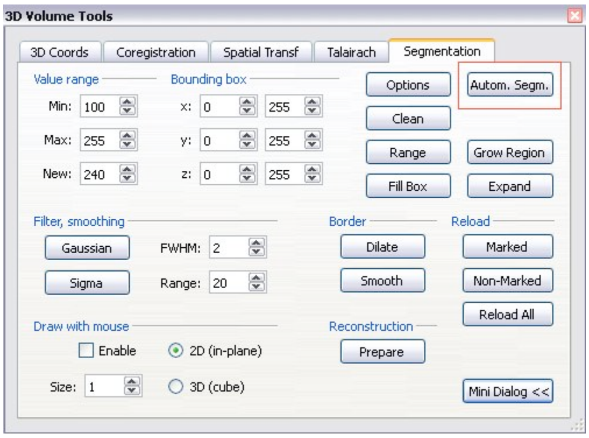


commissure and click Set Point, select AP, adapt the front with Shift+Cursor up/down arrow buttons to a limit when you just see the brain the first time – Set Point, same with PP and posterior point and IP – inferior point Cursor up/down, and RP – right point and LP – Left point – use Cursor left/right. When you have set all points click Save .TAL button. That saves the individual TAL transformation coordinates we need later. [Consult the Getting Started Guide if you are not familiar with the anatomical structures used in Talairach transformations.]

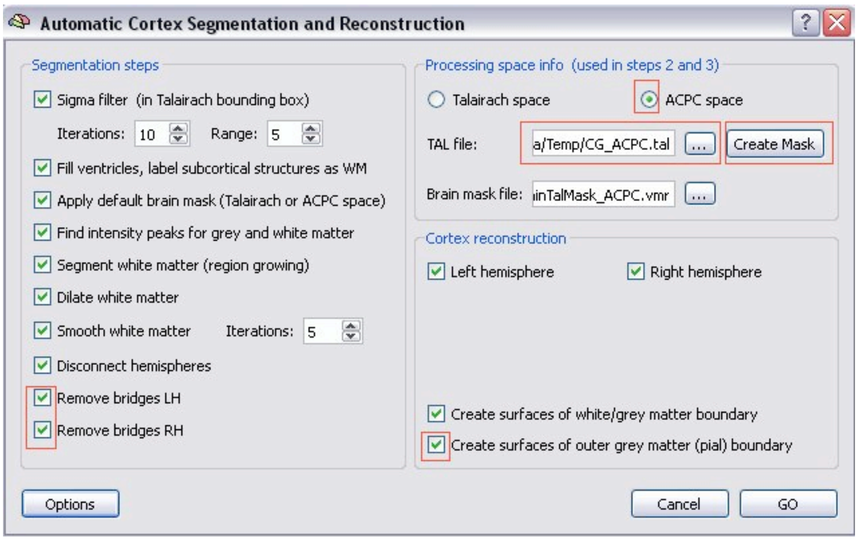
Optional you can generate a true *TAL.VMR by clicking ACPC->TAL button and saving a *_TAL.VMR (with SINC interpolation!).

7. In this step, we will learn how to create advanced **3d renderings of the cortex** with the *Surface Module* of BrainVoyager QX. Those renderings can be used to apply various surface-based techniques like cortex inflation and flattening or surface-based statistics. You need to have loaded the ACPC.VMR.

Go to Segmentation Tab in the 3D Volume Tools. Click Autom. Segm. button.



Select ALL Segmentation Step check marks and all Surface Reconstruction check marks (optional pial/ outer Surface Reconstruction). Switch to ACPC space and load the *.TAL file of the step before. Press the Create Mask button to reconstruct an individual mask file BrainTalMask_ACPC.vmr from the BrainTalMask.VMR file in the BrainVoyager QX program directory. Finally run the automatic segmentation. Confirm or adapt the offered white / grey matter border value.

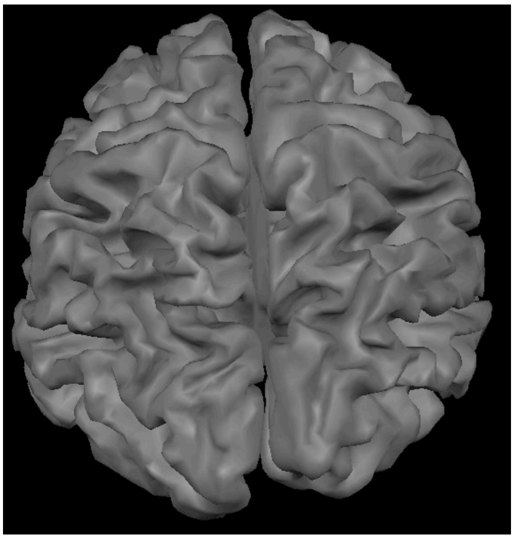


After a while the program will have produced many SRF files. Close all small windows, which appeared.

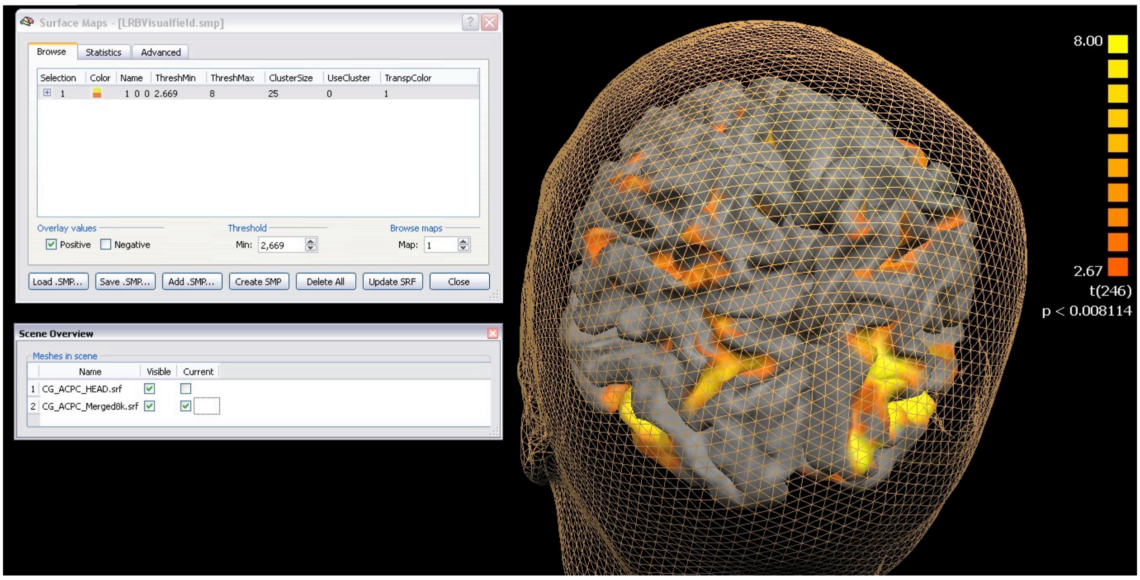
Remark: You can do the segmentation also in TAL space. Then you need to back-transform the Surfaces into ACPC space at Mesh Transformations Menu TAL->ACPC button.

8. Now we will down-sample surfaces of the brain hemispheres to reduce working memory capacities for navigation. Start with the ACPC.VMR and activate the 3D Volume Tools [1st button on the left menu bar]. Press the Surface Module button. At Mesh menu chose Load Mesh, select *_ACPC_LH_RECOSM.SRF. Then select Mesh Simplification at the Mesh menu and down-sample it between 8000 to 12000 vertices resulting in *_ACPC_LH_RECOSM_D8k.srf. Check the mesh density after pressing the wire frame button on the right menu bar (5th button from below, 6th button is closing the mesh.). Do the same with the *_ACPC_RH_RECOSM.SRF.

9. In this step we learn how to merge the hemisphere meshes. You have loaded the down-sampled RH SRF file. Via Add Mesh tab add the LH down-sampled SRF. Go to Scene menu - Merge Meshes in Scene tab and save the file as
 *_Merged_RECONSM_D8K.srf.



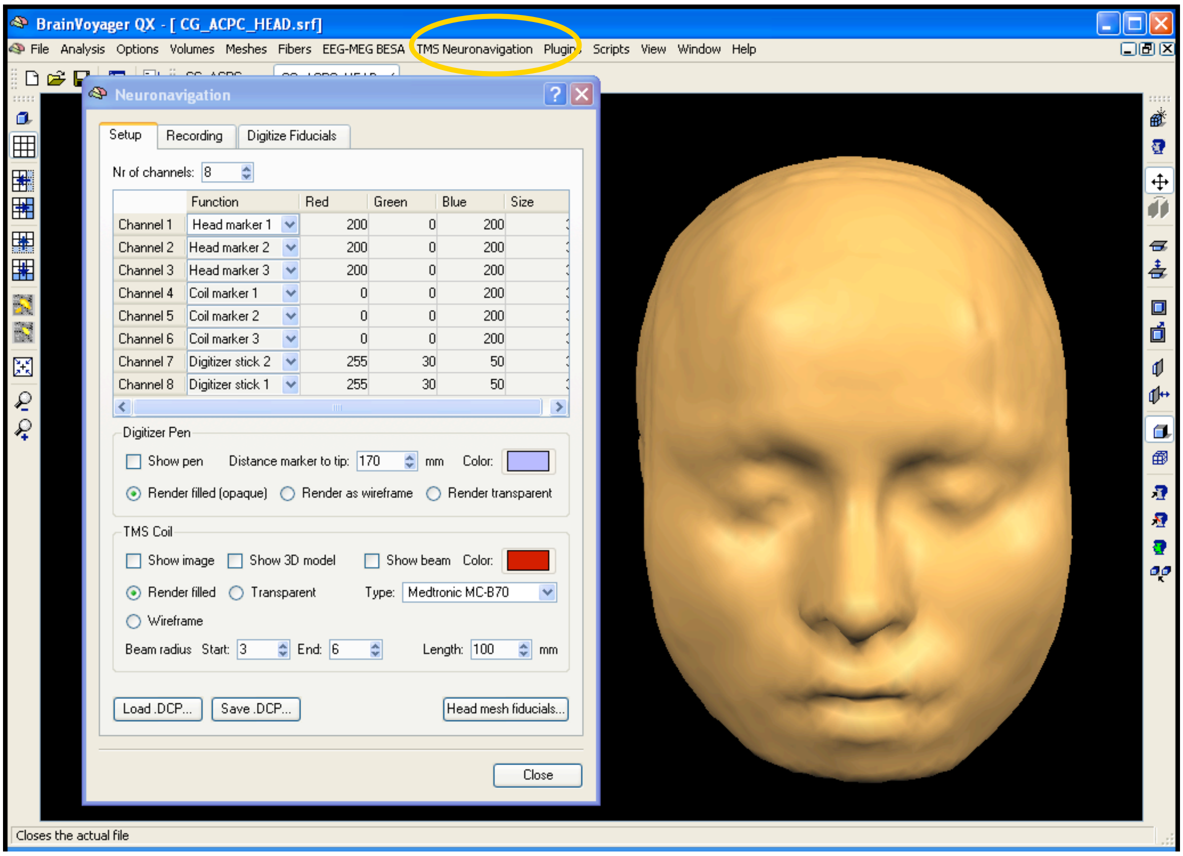
10. Functional imaging data can be superimposed on cortical surface reconstructions in order to neuronavigate the TMS coil based on individual functional brain imaging results. This option allows the definition of a functional region-of-interest, e.g., a brain area that showed increased neural activity during the execution of a particular task, and navigating the TMS coil specifically above this functionally defined target stimulation site.

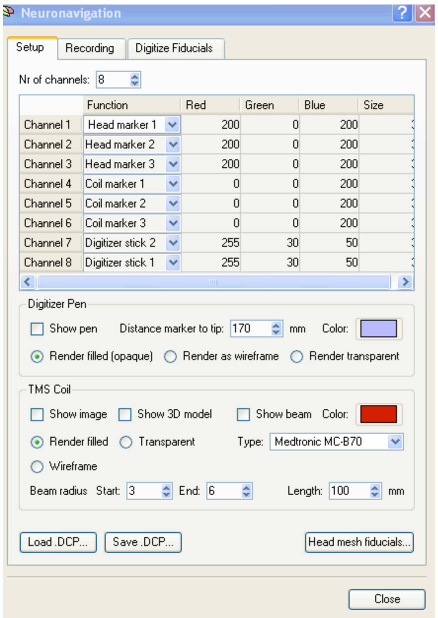


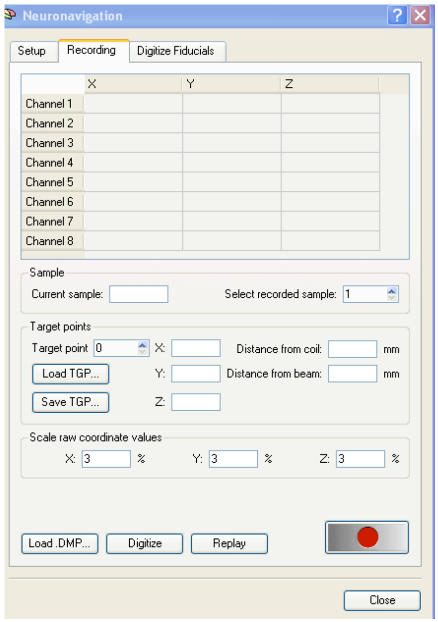
We advise to prepare beside segmentations of cortical surfaces (e.g. grey-white matter or pial boundary reconstructions) and head surface also functional activation maps (GLM, VMP, SMP). For the latter consult the Getting Started Guide and exercise data on the Learning DVD.

STEP 3: The Neuronavigation Module for TMS

To get to the Neuronavigation Module for TMS, you have to start the BrainVoyager QX program. Here you can select the TMS Neuronavigation option on the menu bar (NOTE: The Neuronavigation Module will only open when a mesh file (reconstruction of the head, or cortical surface reconstruction) has been loaded; see Step 2 for details). This module consists of 3 different Dialogue Tabs, namely *Setup, Recording,* and *Digitize Fiducials.*





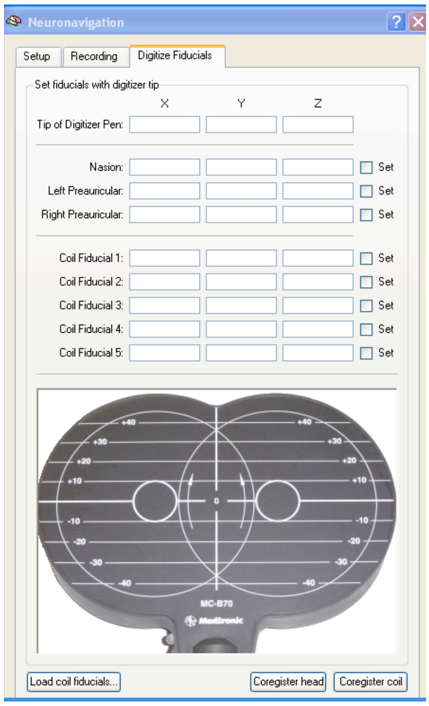


In the *Setup* dialogue you can define general settings such as the visualization of the TMS coil, the "virtual" beam of the magnetic field of the TMS coil or the digitizer pen. And you can select the type of coil you plan to use.

It is recommended to make the coil transparent or apply the wire-frame display for navigation and model the beam concerning length and radius size of start and end point.

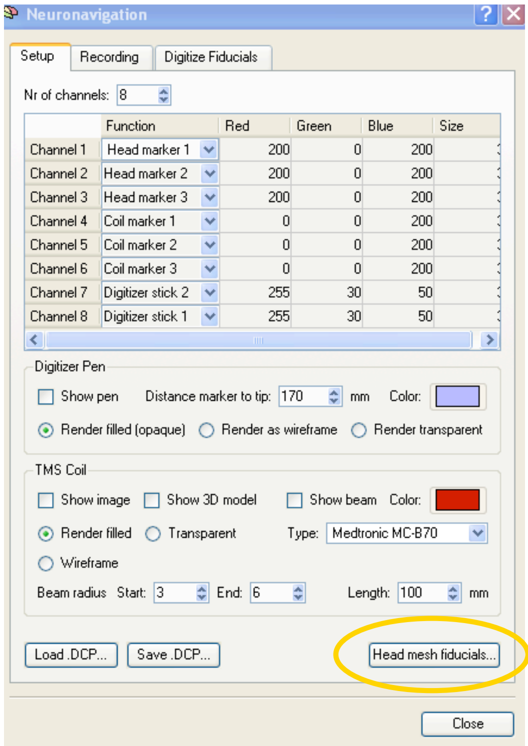
The *Digitize Fiducials* dialogue provides the possibility to coregister head and coil. The picture of the coil seen on the right varies depending on the chosen coil type.

The system can be started at the *Recording* dialogue. Moreover, this menu provides information about the spatial coordinates of each sender.



STEP 4: Defining head mesh fiducials

In this step, anatomical landmarks are defined on the reconstruction of the head.



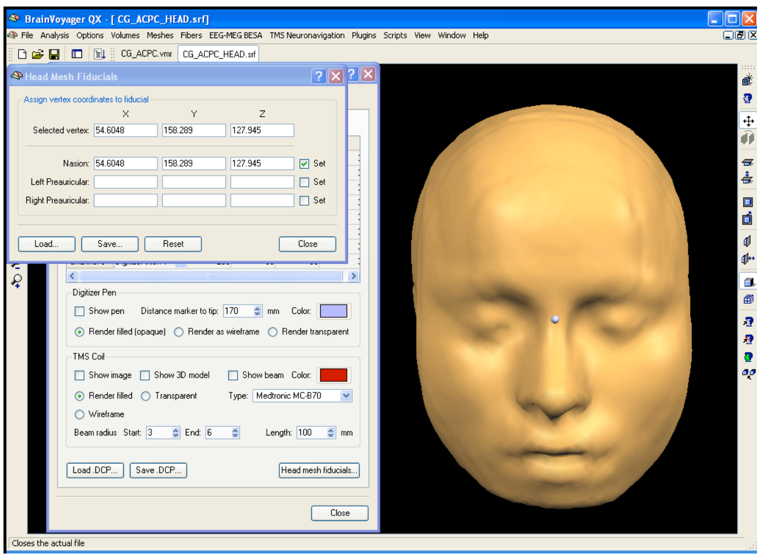
1. Load a VMR in AC-PC space.

2. Load a head mesh.

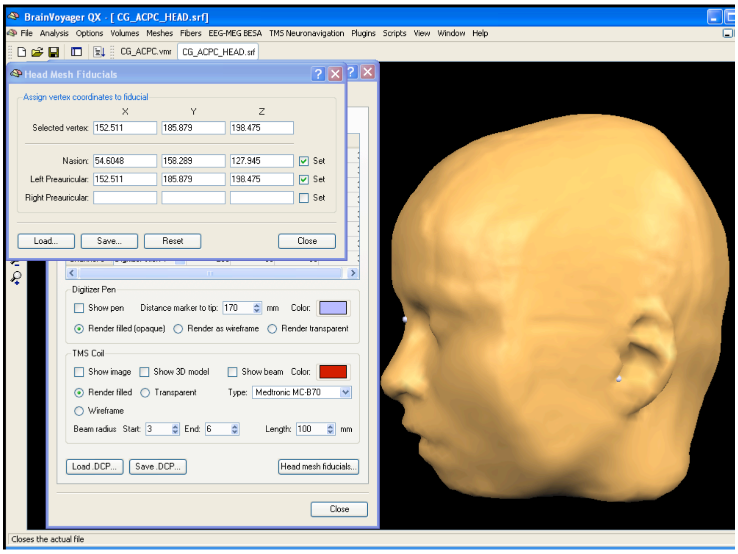
3. Select via the header bar of the program TMS Neuronavigation/ the "Head mesh fiducials" menu or go to the *Setup* section and click the "Head mesh fiducials" button. The Head mesh fiducials dialog will appear.

4. You will now have to select three anatomical landmarks that are easily identifiable on the reconstruction of the head (thus the head mesh) as well as on the participant's real head.

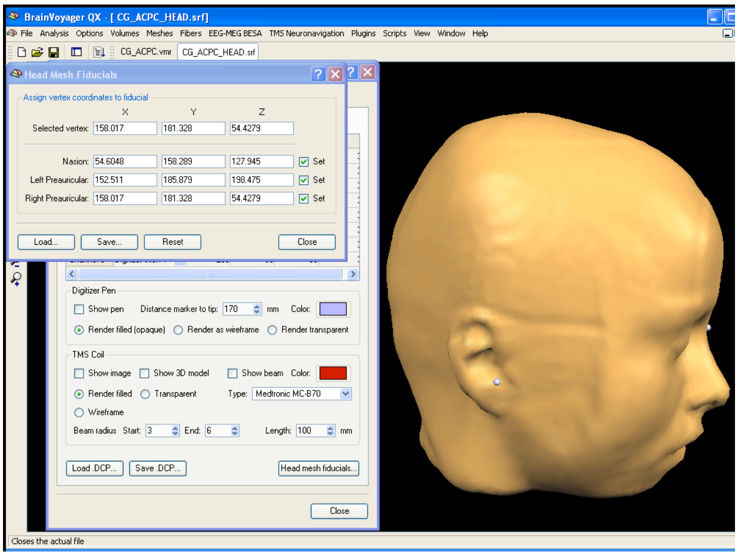
5. To begin with, define a point on the nasion of the head mesh. To mark this point as a fiducial, set the cursor on this point, press Control and click the left mouse button. The coordinates are now automatically filled into the dialog.



6. Thereafter, select a point on the **LEFT** ear of the head mesh. This can be any-where on the ear, as long as this point is easily identifiable on the reconstruction of the head AND on the real head. To mark this point as a fiducial, again set the cursor on this point, press Control and click the left mouse button.



7. Finally select a point on the **RIGHT** ear. To mark this point as a fiducial, set the cursor on this point, press Control and click the left mouse button. The coordinates are also automatically filled into the dialog.



8. It is possible to save these points. This is useful if you want to measure a participant more than one time. To save these fiducials simply click on the “Save” button and give the file an appropriate name. The following session you can load these fiducials by simply clicking on the “Load” button.

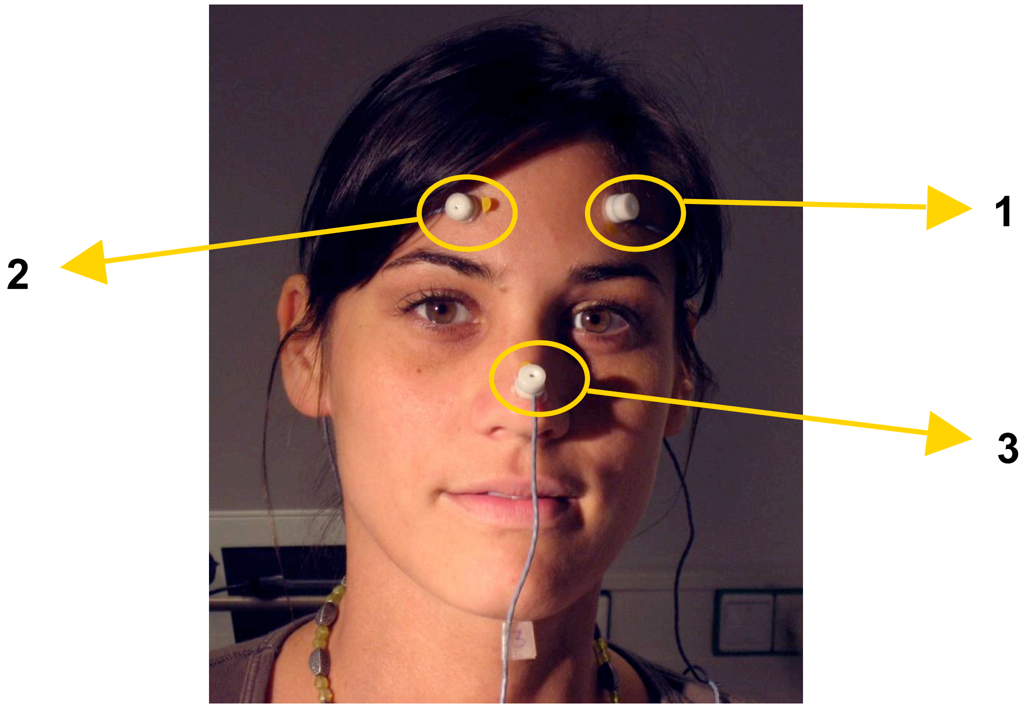
NOTE: Make sure that you do not mix up the order of the definition of the landmarks!

If you would like to change a fiducial, simply click on the green checkmark next to the already defined
point. You will see that the coordinates will then be removed and you can start again with defining the fiducial.

STEP 5: Coregistration of the head

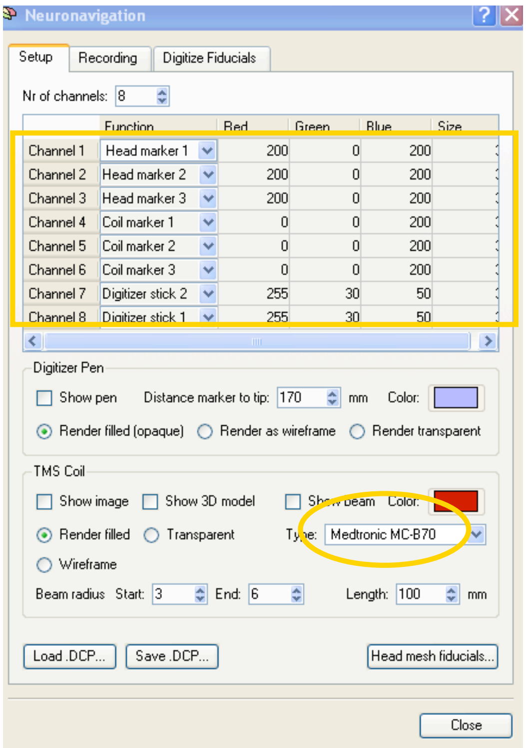
In this step, the participant's real head will be coregistered to the MRI data reconstruction of the head in the software.

1. First the double-sited adhesive stickers have to be attached to the three single head senders. Thereafter, place these senders on the participant's head. The exact position of these senders on the head is not relevant. However, you have to make sure that they form a triangle and that they are not too close to each other. An ideal positioning can be seen in the picture below. Make sure that the order of the senders is as follows: **Sender 1** is on the left side of the participant's forehead, **sender 2** on the right side, and **sender 3** is on the nose. The number of the senders can be found on a sticker at the end of each cable.



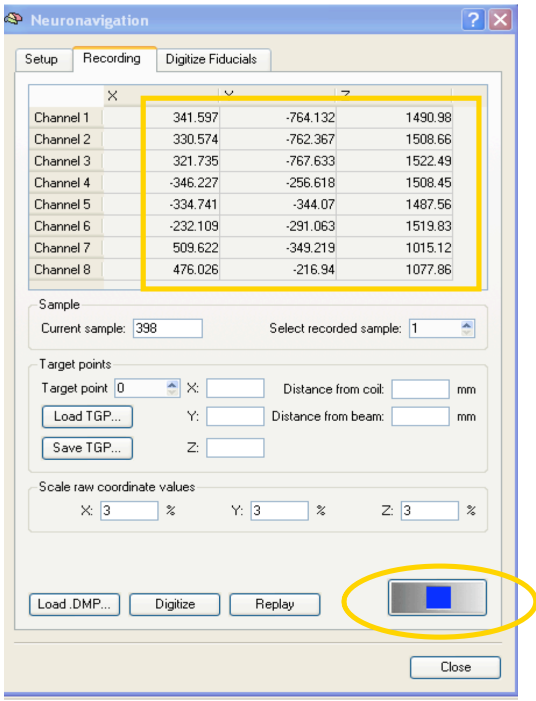
NOTE: Once the head senders are attached, they may not be moved anymore. In case a sender falls off during the recording, you will have to attach the sender again and restart the registration! The adherence of the senders can also be seen in the short video clip "Head sender attachment".

2. Before the system can be started, you have to select the TMS coil type that you plan to use. Go to the Setup section of the Neuronavigation dialog. At the TMS Coil tab you can choose the exact type of TMS coil.



3. After the 3 head senders are placed and the coil model is chosen, the system can be started. Go to the *Recording* tab and click the button with the red circle, which will turn into a blue square to signal the active status.

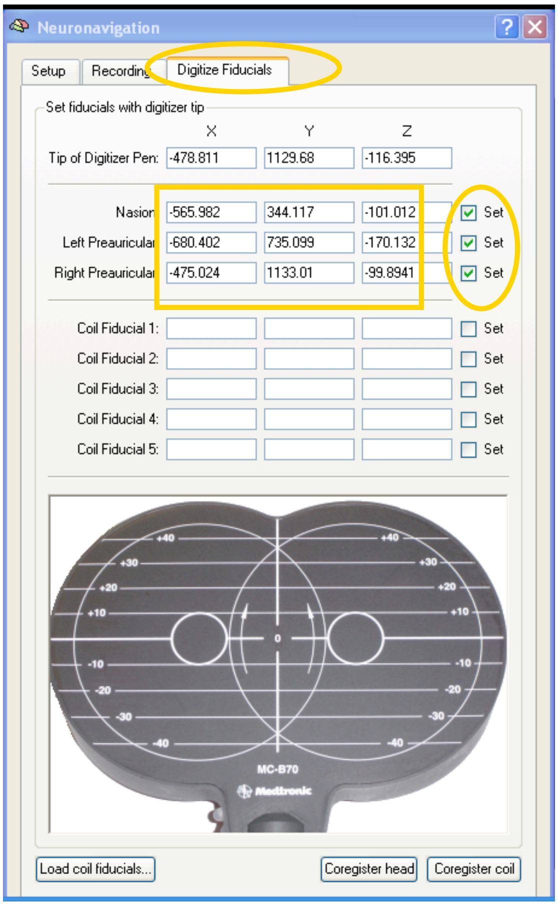
A window will appear, in which you can choose the hardware driver necessary to start the system. The correct hardware is picked by default.



Therefore you only have to press OK. After a few seconds you will hear the different senders emitting ultrasonic pulses.

NOTE: The spatial coordinates of the senders can be seen in the *Recording* section. The display will show only the coordinates of intact senders, which are in contact with the microphone.

4. In the next step, the anatomical landmarks previously defined in the head mesh have to be identified on the participant's real head. To do this, choose the *Digitize Fiducials* section.

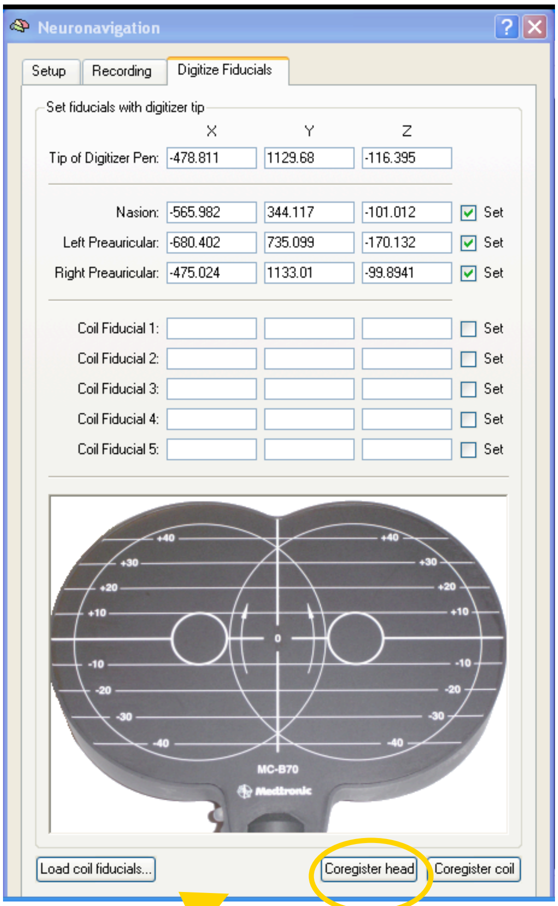


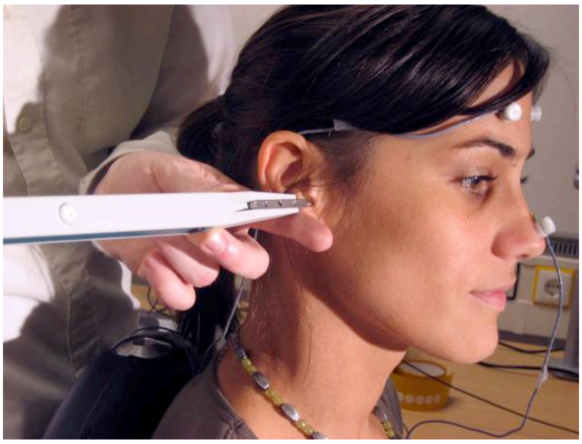
5. Take the Digitizer Pen and put its pointer on the same point at the participant's nasion as previously defined on the head reconstruction. Once you are at that point, click the button of the pen "shortly" (like a mouse click). Then the box next to the "Nasion row" gets a check mark and the spatial coordinates of this point are saved.

Do the same with the ear points. Make sure that the coordinates of the tip of the Digitizer Pen are always displayed in the window. If they are not displayed, the senders of the Digitizer Pen do not have contact to the microphone and the coregistration cannot take place.

6. Now take the Digitizer Pen and put its pointer on the same point at the participant's **LEFT** ear as previously defined on the head mesh. Once you are at that point, click the button and the box next to the "left Preauricular line" is check marked. The spatial coordinates of this point are also saved now.

7. Finally, put the pointer of the Digitizer Pen on the same point at the participant's **RIGHT** ear as previously defined on the head mesh. Once you are at that point, click the digitizer button and the box next to the "right Preauricular row" receives the check mark. The spatial coordinates of this point are also saved now.

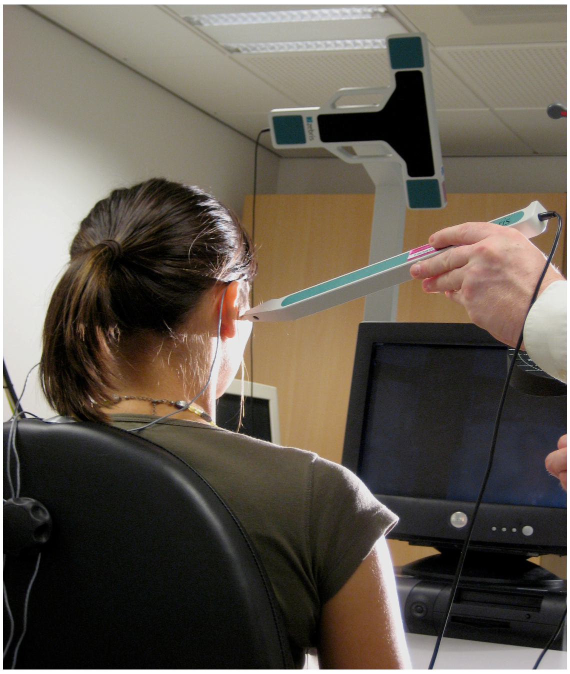




8. After setting all three fiducials press the button "Coregister head" in the *Digitize Fiducials* section. The white and red fiducials should fall on each other. Then the participant's real head is coregistered perfectly to the reconstruction of the participant's head.

NOTE: During this coregistration, all the senders have to have contact with the measuring device (thus the head senders and the senders of the Digitizing Pen). Be careful that nothing (e.g. fingers) interrupt this contact.

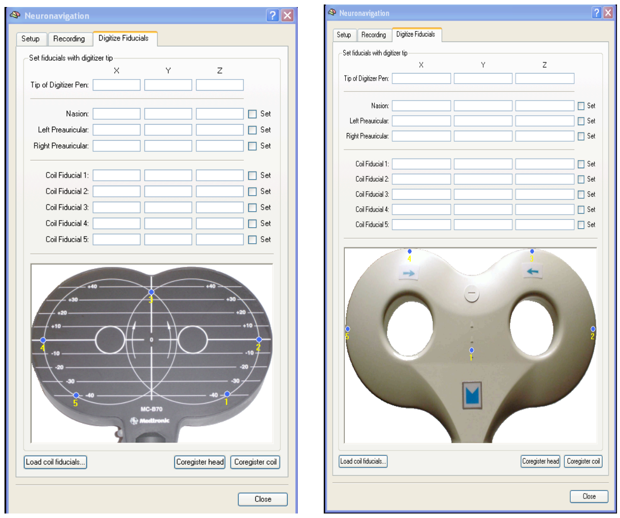
Use the wire frame display for the head model to check the fiducial localization.



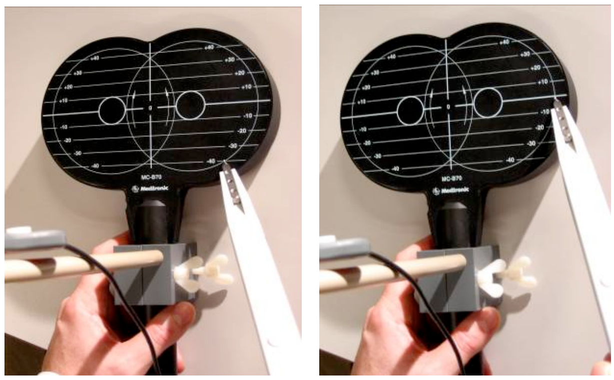
STEP 6: Coregistration of the TMS coil

After having coregistered the participants head, the next step concerns the co-registration of the TMS coil.

1. To do this, chose the *Digitize Fiducials* section. Here you will see a picture of the coil that you selected earlier. Take the Digitizer Pen and put its pointer on the real coil on the first point as displayed in the picture.

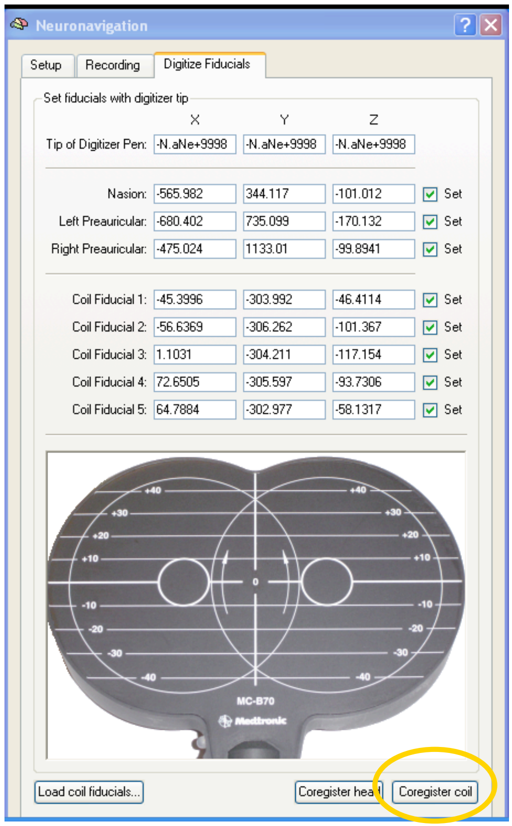


NOTE: The points differ between coils. Once you are at the first point, click the box next to the "Coil Fiducial 1 row". The spatial coordinates of this point are now saved. Do this for all the other points.



Again make sure that the coordinates of the tip of the Digitizer Pen are always displayed in the window. If they are not displayed, the senders of the Digitizer Pen do not have contact to the measuring device and the coregistration cannot take place

2. After you have set all coil fiducials, press the button "Coregister coil" in the *Digitize Fiducials* section. Now, the coil is coregistered.



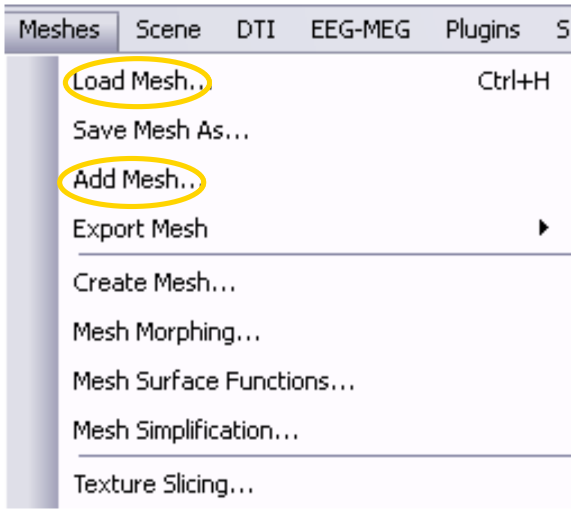
NOTE: Also during this co-registration, all the senders have to have contact with the measuring device (thus the head senders and the senders of the Digitizing Pen). Be careful that nothing (e.g. fingers, people) interrupts this contact.

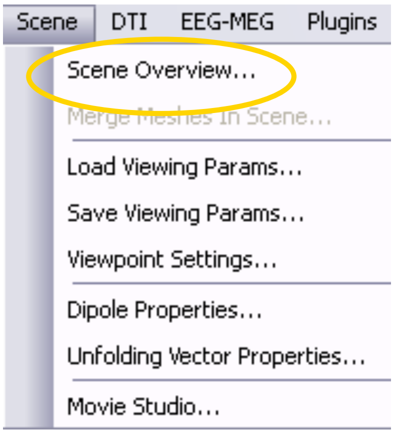
The coregistration of the coil can be seen in the short video clip "Coil co-registration".

STEP 7: Real-time neuronavigation to an anatomical target site and a functional region of interest

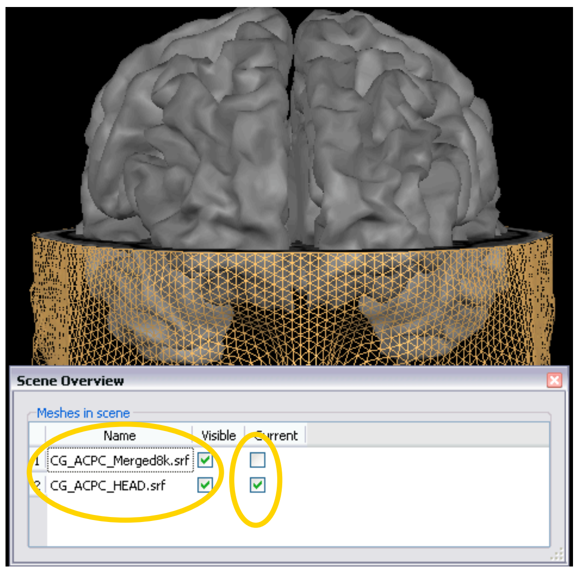
In this step you will learn how to navigate a TMS coil based on individual analyzed and visualized anatomical and functional MRI data of the head and brain. Our goal is to neuronavigate on the head mesh with the underlying cortex reconstruction.

1. After starting BrainVoyager QX you need to load the *_ACPC.VMR of your subject, the head mesh *_ACPC_HEAD.SRF and add the segmented cortex mesh(es) - either both hemispheres or the merged mesh of them.



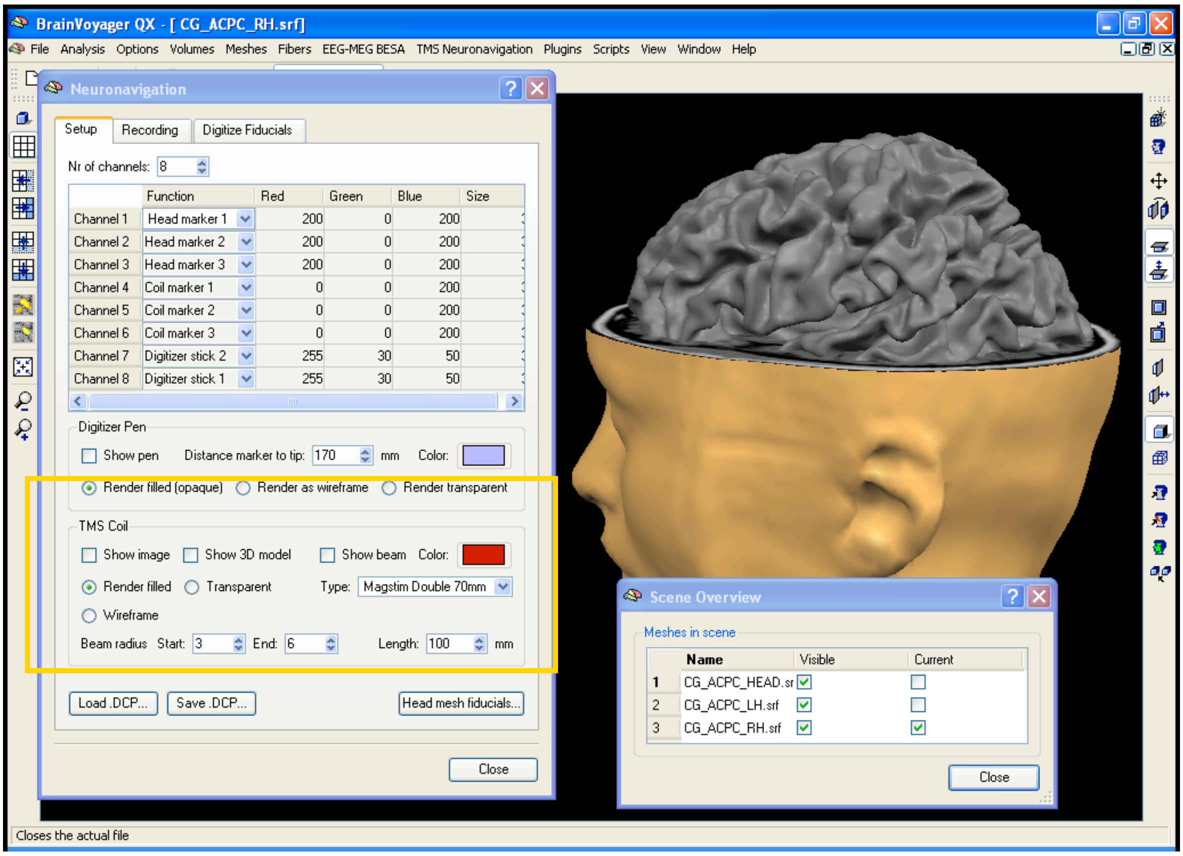


2. To activate one of the selected meshes, go to “Scene” → “Scene Overview”. In the scene overview dialogue you can choose whether selected meshes shall be visible (“Visible”) or not. Moreover, you can activate one of the meshes (“Current”) if you like to apply certain functions to the selected mesh like cutting, wire frame display, overlay of functional data, or setting a navigation target point as we see later.

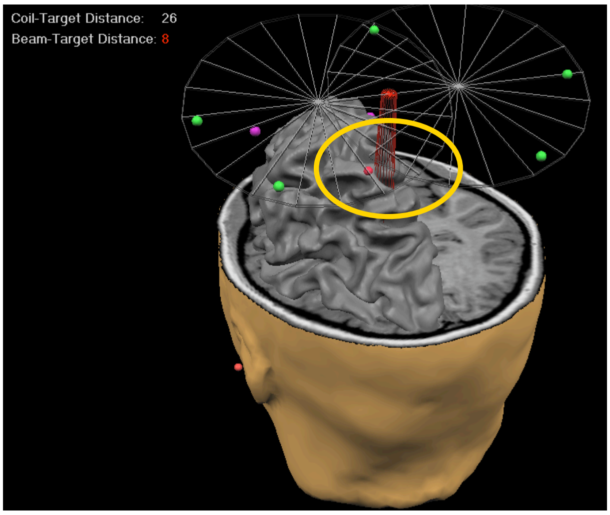


7.1 Real-time neuronavigation to an anatomical target site

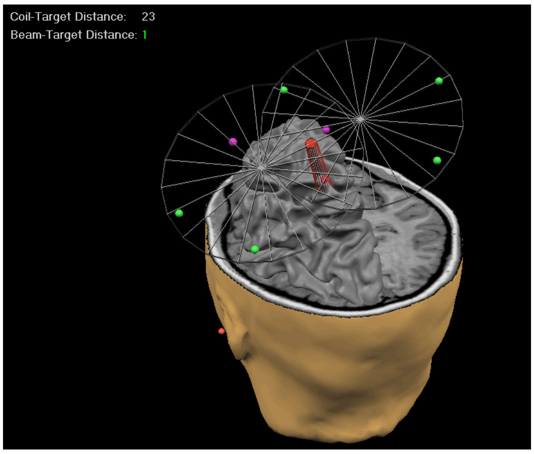
1. Select a segmented cortex mesh and identify your relevant anatomical target site. To mark this site as target point, set the cursor on this point and click the right mouse button. Choose the option “Set Target Point”. You will now see a red dot on this point.



2. Go to the *Recording* section of the Neuronavigation dialog. Choose Target point 1 in the Target point section.

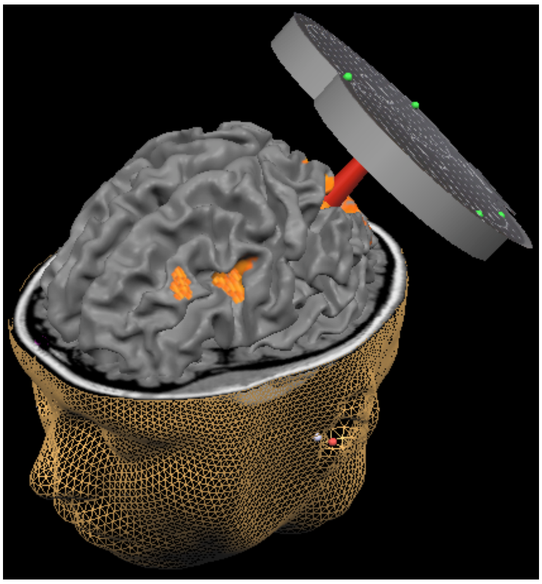


3. The target point is now activated. You will see the Coil-Target Distance and the Beam-Target Distance in millimeters on the top left of the surface module. If you aim approximately on the target point, the distance information turns green. If you are too far away, the information is either yellow or red.



7.2 Real-time neuronavigation to a functional region of interest

1. Create or load your functional activation map (GLM - VMP or SMP File; see BrainVoyager QX Getting Started Guide) and identify your functional region-of-interest. Navigate the TMS coil based on the functional activation data of your participant. To obtain information about Beam-Target distance etc, set a Target point on the functional region-of-interest (CTRL+left mouse click). You can also save its coordinates as *.TGP.



TIP: Depending on the location of stimulation target site and/or the perspective of the head mesh, it might be useful to change the visualization of the TMS coil into, e.g. the transparent mode. This can be done in the *Setup* section by deselecting the “Show image” option and checking the “Transparent” option.