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## Multimodal imaging of recovery of functional networks associated with reversal of paradoxical herniation after cranioplasty

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### Abstract

Cranioplasty following decompressive craniectomy is reported to result in improved blood flow, cerebral metabolism, and concomitant neurological recovery. We used multimodal functional imaging technology in a patient with marked neurological recovery after cranioplasty, specifically, imaging of functional MRI resting state networks, auditory responses, and cerebral metabolism before and after cranioplasty. Significant functional changes observed in the images correlated with the subject's neurological recovery. Our results suggest a link between recovery of cerebral metabolism and intrinsic brain mechanisms of cerebral vascular integration and resting state networks identified with functional MRI following cranioplasty.

### Keywords

Cranioplasty; resting state functional MRI; functional MRI; positron emission tomography

## INTRODUCTION

Management of patients after severe brain injury often includes the temporary removal of skull bone (craniectomy) in the acute stage to mitigate the effects of brain compression due to a variety of processes that may increase intracranial pressure. Replacement of the skull (cranioplasty) may lag the acute phase considerably, and case reports and case series have indicated that the cranioplasty procedure results in improved blood flow, cerebral metabolism, and concomitant neurological recovery (1-3). More generally, recovery of

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integrative brain function after severe injuries resulting in a minimally conscious state (MCS) remains poorly understood with behavioral recovery typically occurring over many months (4) or even years (5). As a result of the slow time course of recovery and the potential for cognitive recovery to proceed in the absence of overt motor behavior (6) it is increasingly recognized that quantitative or neurofunctional measures are needed to more precisely track the evolution of recovery (7,8). Here we measured fMRI auditory response, resting state networks (RSNs), and fluorodeoxyglucose positron emission tomography (FDG-PET) before and after right-hemispheric cranioplasty in a severely brain injured subject who emerged from MCS following the procedure.

In resting state fMRI, subjects undergo a conventional fMRI imaging protocol without performing specific cognitive or motor tasks. The resulting blood-oxygen-level-dependent (BOLD) signal contains various resting state network patterns, obtained by algorithms that compute and segment correlations in the signal (9-12), and putatively revealing information about connectivity of the cerebral neuro-vascular network. Although neither the physiological origins of resting state signals nor their potential clinical utility have been completely characterized yet, during the past five years a broad of clinical applications of resting state fMRI have been investigated (13). The most prominent resting state network, the “default mode,” was originally discovered in resting metabolism (PET) data (12) and later confirmed in conventional fMRI studies (14), and is thought to reflect the existence of an organized, baseline default mode of brain function. It is also thought to be involved in consciousness on a more basic level since it partially disintegrates during deep sleep (15). In addition to the default mode network, several other resting state networks have been identified more recently (16,17), and a direct correspondence demonstrated between their BOLD signals and fluctuations in EEG oscillations (16,18-20). Further, theoretical modeling attempts of the dynamics of RSNs, for example by means of numerical coupled oscillator networks (21), will lead to a deeper understanding of the relationship of clinical RSN observations and pathologies of intrinsic brain dynamics such as disturbances in conduction delays.

### Case report

Six months prior to the first imaging study reported herein the subject, a 19 year old female, suffered a severe traumatic brain injury following a fall from the front of a moving vehicle. Initial examination in the field revealed signs of central herniation with bilateral pupillary dysfunction with a Glasgow Coma Scale (GCS) of 3. Emergency management included acute evacuation of a left epidural hematoma and bilateral craniotomies. Intracranial pressure monitoring showed average ICP of 30 mmHg. Over next five month period following acute injury the patient demonstrated inconsistent evidence of response to environmental stimuli as documented in medical records which did not improve after a placement of a ventriculoperitoneal shunt in the second month after injury. One month prior to the first imaging study (six months after injury) the patient underwent a left sided cranioplasty with subsequent recovery of reliable command following to simple motor commands. On admission to our study the patient’s neurological exam was notable for 4 mm pupils bilaterally reactive to 2 mm, a left upward gaze preference with occasional spontaneous nystagmus and increased range of movement to left with passive oculocephalic stimulation. Grip strength of 2/5 was noted bilaterally with no withdrawal of the right upper extremity to noxious stimuli and spontaneous withdrawal of the left upper extremity; lower extremities revealed bilateral spastic contractures with hyperreflexia. Formal quantitative behavioral assessment at the time of the first study reported here demonstrated an exam consistent with minimally conscious state (MCS) including reliable auditory command following and intermittent gestural communication. The Coma Recovery Scale Revised (CRS-R (22)) best total score was 14 (patient demonstrated consistent following of auditory

commands, visual tracking despite a lack of blink to direct threat, object manipulation with the right hand, absence of vocalization or oral movement, inconsistent and inaccurate yes/no responses with right thumb, and eyes open state without stimulation). The second imaging study was done ten months after injury and two months following a right sided cranioplasty. At this time, the patient demonstrated further improvements on quantitative behavioral examination including recovery of functional object use (demonstrate using her right hand and upper extremity of the function use of common objects), vocalization to command, consistent communication (accurate yes/no responses through gesture), and improved attentional function with consistent responses to examiner queries (CRS-R total score of 20). At the time of this second evaluation formal testing indicated emergence from MCS based on sequential examination demonstrating consistent and accurate communication on simple situational accuracy questions.

## MATERIALS AND METHODS

An institutional review board approved consent declaration was obtained from the patient's legally authorized surrogate under active approved protocols. The imaging protocols for both study time points were identical. RS and auditory fMRI was performed, together with anatomical MRI, on a 3.0 Tesla General Electric Medical Systems (GEMS; Waukesha, WI) clinical MRI system with an eight-channel head coil using echo-planar imaging based functional MRI pulse sequences (repetition time TR = 2 s, echo time TE = 30 ms, flip angle 70, matrix size  $64 \times 64 \times 28$ , axial field of view 24 cm, 5 mm slice thickness; RS fMRI was acquired with 180 samples, auditory fMRI with 128 samples). Before RS fMRI, the subject was instructed to think of nothing in particular; during auditory fMRI, the subject was instructed over headphones to imagine herself swimming and to stop imagining herself swimming, for eight times each. The data was analyzed with BrainVoyagerQX (Brain Innovation B.V., The Netherlands; motion correction, smoothing, detrending, re-sampling) and by using independent component analysis (RS-fMRI) and general linear modeling (auditory fMRI) including motion parameters as nuisance variables. In this model, the auditory instructions (and not the imagery periods in between) were used as stimuli. Fluorine-18 FDG-PET was performed on a GEMS combined PET-CT LS Discovery unit. Images were acquired in dynamic high-sensitivity emission mode (matrix size  $128 \times 128 \times 35$ , axial field of view 25 cm, 4.25 mm slice thickness). Standard uptake values (SUV) were computed from the PET data including CT based skull attenuation corrections and then co-registered to high-resolution MRI images using PMOD (PMOD Technologies Ltd, Switzerland) and visualized using Mricron (Chris Rorden).

## RESULTS

### Anatomical changes

Before cranioplasty, anatomical MRI shows an overall loss of brain symmetry due to distortions with marked evidence of sunken skin flap depression on the side of the craniectomy (Figure 1, left panels). T1 weighted images show hyperintense cortical contusion with laminar necrosis. T2 weighted FLAIR images show anterior temporal, inferior frontal, and bilateral occipital injury. After cranioplasty, symmetry seems to be only slightly restored. Structural imaging shows serosanguinous collection underlining cranioplasty and new small subdural collections surrounding both hemispheres (Figure 1, right panels). A detailed comparison of the two brain images after co-registration reveals that ventricular spaces are markedly reduced after cranioplasty (not shown).

### Resting state network changes

Out of the six resting state networks (16), in this subject three networks were found before and after cranioplasty, namely the default mode, the dorsal attention, and the sensory-motor network. The visual and the self-referential networks could not be found in either case. The auditory-phonological network only showed up post-cranioplasty. Parametric maps of resting state network connectivity are provided in Figure 1. (For comparison, a study with nine normal control subjects using the same methodology resulted in a 93% reliability of network identification (H.U.V., unpublished)). Overall, the networks that existed at both time points increased in volume or remained unchanged: default mode +40% (from 52 to 73 ccm), dorsal attention -2% (from 56 to 55 ccm), and sensory-motor +46% (from 67 to 98 ccm).

### Auditory response changes

Before cranioplasty, auditory responses to short spoken sentences were found mainly in left primary auditory areas and were mostly absent on the side of the craniectomy. After cranioplasty, strong auditory responses were found bilaterally (Figure 1, bottom two rows).

### Resting metabolism changes

A marked increase in standard uptake values of FDG was observed after cranioplasty. Whole brain averaged SUVs (excluding the cavity at the second time point) increased from  $2.5 \pm 2.0$  to  $3.0 \pm 2.4$  g/ml [ $\pm$  standard deviation]. Regional changes were observed in left mesial frontal regions and within the mesodiencephalon (upper brainstem and thalamus) (Figure 2, arrows).

## DISCUSSION

We have found signatures of increased functional activity using three different functional imaging modalities in a subject following cranioplasty to repair a sinking flap produced after decompressive craniectomy. FDG-PET measurements indicated both global increases in cerebral metabolism and marked local improvements in mesodiencephalic region; resting state and auditory functional MRI revealed more specific information about neuronal network functional connectivity. We have previously identified loss of RSNs in the setting of specific neurovascular injuries (13) with lesioned neuronal substrates, but the re-appearance of the auditory resting state network after cranioplasty along with a significantly enhanced auditory response on the ipsilateral side is novel and points towards further clinical significance of RSN imaging in addition to previous findings. Some RSNs are robust to anesthesia (23,24) and light sleep (25) suggesting that intrinsic neurovascular coupling contributes to them. Prior studies have identified reversible changes in neurovascular coupling using electroencephalography measures and FDG-PET in the minimally conscious state (26). Taken together, these observations may relate to aspects of recovery of cerebral autoregulation mechanisms and raise the possibility that RSNs *per se* reflect a key aspect of the spatiotemporal regulation of intracranial blood volume, observed as the constancy of cerebral blood pressure across wide ranges of systemic blood pressures.

Our finding of reduced resting state network connectivity on the side of the craniectomy can be directly related to a prior demonstration of reduced EEG network coherence in the lesioned hemisphere in a vegetative patient with severe asymmetric subcortical brain damage associated with the loss of thalamic input (27). Measurement of RSNs is based on the coherence of BOLD signals and both findings may reflect damage to thalamo-cortical loop connections, likely a strong source of EEG coherence (28) as well as of resting state network connectivity (29,30). Improvement in the auditory RSN seen here may thus associate with our findings of reversal of depressed resting metabolism in the thalamus

following cranioplasty. Subject motion can conceal functional activations and resting state network components and should always be considered in interpreting data from subjects that are not fully cooperative and thus on average move more than healthy control subjects. In this study head motion was more pronounced at the second time point for the functional scan and at the first time point for the resting state scan. Therefore, it cannot account for the common trend observed in both scans alone.

The marked increase in regional cerebral metabolism (FDG-PET) in the left mesial frontal regions and within the mesodiencephalon of the left hemisphere before and after the cranioplasty is of particular note. This finding suggests a partial resolution of a component of “paradoxical herniation” originating from the earlier craniectomy. Prior studies have demonstrated a mesodiencephalic herniation syndrome resulting from the effects of atmospheric pressure and gravity in the setting of craniectomy (31-33).

Bilateral improvements of regional cerebral blood flow after cranioplasty have been shown before in perfusion (3), dynamic (34), and Xenon-enhanced (35) CT imaging. Our study demonstrates the potential utility of resting state MRI and functional MRI, both of which can be easily added to conventional clinical MRI protocols without the need of an additional imaging session. In our patient, significant increases in the volume of some RSN components and both global and regional cerebral metabolism measured using FDG-PET correlated with the subject’s neurological recovery. Notably, the auditory RSN, absent before cranioplasty, reappeared afterwards, a novel observation that suggests a link between intrinsic brain mechanisms of cerebral vascular integration and the RSN response. The findings support the role of cranioplasty in restoring aspects of integrative cerebral function after severe brain injuries and provide further insight into the physiological basis of the RSN.

Our results suggest the potential utility of these functional measures to track recovery following decompressive craniectomy procedures; the procedure has become an increasingly frequent part of the neurocritical care of patients with severe brain injury and has wide application in the clinical management of increased intracranial pressure arising in the setting of different types of brain insult (31). Such physiological assessments of recovery during post-operative management after craniectomies are likely to be particularly important for patients with severe brain injuries or the elderly who may recover slowly from their injuries (36).

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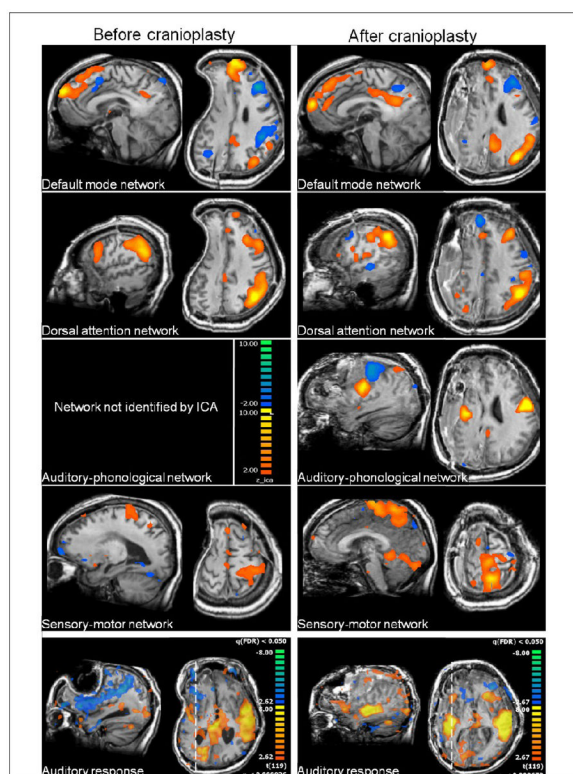
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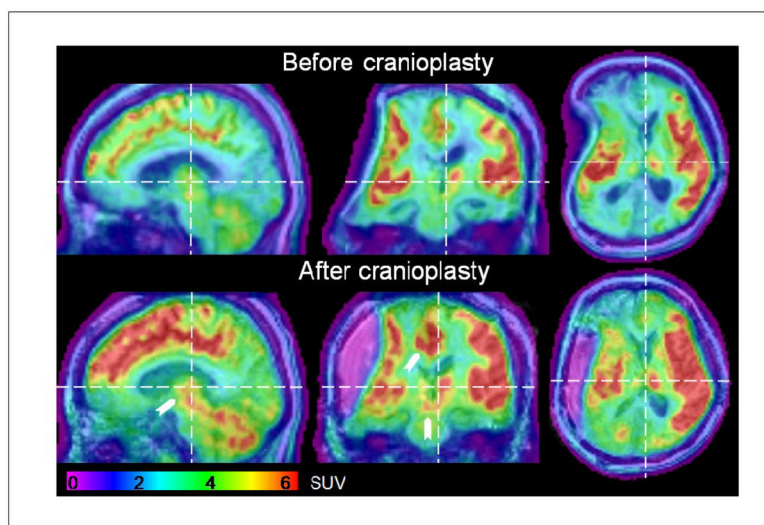
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**FIGURE 1.**

Top four rows: Resting state networks before (left column) and after (right column) cranioplasty. The auditory-phonological network could not be identified by independent component analysis (ICA) before cranioplasty and emerges only post-surgery. Colors denote z-values for the independent components as shown on the scale in the third row on the left. Bottom row: Auditory responses to stimulation with short spoken sentences before (left) and after (right) cranioplasty. Before cranioplasty, auditory response is absent on the ipsilateral side and restored after cranioplasty. Colors denote z-values of the general linear model used to fit the response. The threshold is defined as a false discovery rate of the multiple test problem of  $p = 0.05$ . Dashed lines on the axial cuts denote the position of the corresponding sagittal images. Axial cuts are shown in radiological convention in which the right side of the brain is shown on the left side of the image.





**FIGURE 2.**

FDG-PET images before and after cranioplasty overlaid onto anatomical MRI images. Color codes standard uptake values (SUVs) in units of g/ml as shown in the color bar at the bottom of the panel and arrows point towards changes in mesodiencephalic and mesial cortical regions. Dashed lines mark the position of the corresponding other cuts. Axial and coronal cuts are shown in radiological convention.