Simultaneous Dynamic and Functional MRI Scanning (SimulScan) of Natural Swallows

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In studies of swallowing, dynamic and functional MRI are increasingly used to observe motor oropharyngeal behaviors and identify associated brain regions. However, monitoring of motor performance during a functional examination requires disruptive monitoring sensors, visual or auditory cued tasks, and strict subject compliance to stimuli. In this work, a simultaneous acquisition (SimulScan) was developed to provide dynamic images to monitor oropharyngeal motions during swallowing (1 mid-sagittal slice at 14.5 frames per second) simultaneous with functional MRI (24 oblique-axial slices with a TR of 1.6512 s). Data were acquired while three healthy adult subjects passively viewed a movie during three 15-min scans with the purpose of covertly studying uncued natural swallows. Dynamic MR images were used to determine timing of swallow onsets for subsequent functional analysis. Resulting functional maps show significant areas of activation that agree with previous functional magnetic resonance imaging studies of cued water swallows, except for regions associated with processing the task stimulus. SimulScan may prove a useful tool in developing new techniques for studying swallowing and associated neuromuscular disorders. Magn Reson Med 65:1247–1252, 2011. © 2011 Wiley-Liss, Inc.

Key words: functional MRI; dynamic imaging; swallowing; pulse sequence design

INTRODUCTION

Swallowing is a complicated coordination of central and peripheral sensorimotor behaviors that is necessary for sustaining life. Nearly 40 pairs of bilaterally innervated muscles must be activated in proper sequence for a completely functional swallow. This coordinated process transforms the aerodigestive tract from a path for air movement, to a duct for food and fluids (1). The transformation seals the tract, preventing nutritive materials from entering and clogging the airway during its transportation to the pharynx. Fundamental to proper swallowing is involvement of cortical, subcortical, and brainstem areas. Dysphagia, i.e., difficulty swallowing, may result from failure in the central neural and peripheral sensorimotor systems, and may lead to malnutrition, dehydration and respiratory problems (1). Risk for dysphagia increases with age, and it can be caused by numerous neurogenic diseases such as stroke, dementia, Alzheimer's Disease, Parkinson's Disease, cerebral palsy, and traumatic brain injury (2).

MRI has proven to be a useful tool for studying both the central and peripheral sensorimotor levels of swallowing using both functional MRI and dynamic imaging. MRI research of swallowing and dysphagia has increased dramatically over the last decade and continues to provide promising results in understanding the mechanisms of age- and pathology-related changes. Cortical control of swallowing has been evaluated with functional MRI (2–6), and oropharyngeal muscle behaviors have been studied by dynamic MR imaging (7–14). However, few MRI studies have looked at integration of the neural control and oropharyngeal sensorimotor function, although such integrated studies may hold the key to studying more nuanced swallowing changes such as aged swallowing, i.e., presbyphagia (1), and difficulty in planning deglutition, i.e., swallowing apraxia (15). Understanding the interaction between the central and peripheral sensorimotor behaviors could provide breakthrough clinical knowledge for patients with neurogenic dysphagia. To correctly identify and treat neurogenic swallowing disorders, a clear link must be made between neural activation and the corresponding sensory responses and muscle activations (2).

Dynamic MRI of swallowing visualizes soft tissues better than X-ray video fluoroscopy, where dense bone may obscure underlying soft-tissue movement. Additionally, X-ray fluoroscopy also requires use of ionizing radiation and a contrast agent (barium) must be swallowed for accurate judgments of the biomechanics of the swallow (16). A current significant advantage of X-ray fluoroscopy over MRI is its imaging speed, obtaining rates of 30 frames per second or faster. In contrast, MRI dynamic imaging has only recently achieved serial imaging rates of 20 frames per second with an optimized acquisition sequence (13,14). Imaging speeds at this rate or faster are required to temporally resolve many of the complex motions during swallows. For instance, velar elevation during swallowing is achieved in ~ 50 ms and velopharyngeal contact during the pharyngeal stage of swallows has been reported to take between 300 to 400 ms (17).

Besides imaging speed, another challenge for fast imaging with MRI in this region includes magnetic susceptibility differences that exist at air-tissue interfaces, which are abundant in the oropharyngeal region. The

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Received 1 September 2010; revised 23 December 2010; accepted 3 January 2011.
DOI 10.1002/mrm.22824
Published online 28 February 2011 in Wiley Online Library (wileyonlinelibrary.com).

susceptibility differences result in artifacts that depend on the sequence design. Susceptibility artifacts can be addressed in the acquisition, by splitting an acquisition into multiple shots, or during image reconstruction by using a susceptibility corrective reconstruction algorithm.

Functional MRI noninvasively monitors brain activations associated with a performed task by examining local changes in blood oxygenation (18). Often the task is cued by visual or audio stimulus, instructing the subject when and what task to perform. The subject must perform the task in strict compliance with the stimulus for accurate fMRI statistical analysis. In fMRI studies investigating swallowing, secondary-monitoring devices including surface electrodes placed over the thyroid cartilage (6) or pneumographic belts placed around the neck (2,3), ensure the subjects' swallows comply with the stimuli. Such devices may result in sensory feedback, interfering with normal muscle function, motor planning, and even brain activations. Alternatively, swallowing compliance may not be monitored. This is problematic as missed or delayed swallows may alter fMRI statistical results. Dynamic MRI images of the oropharyngeal region acquired simultaneous with fMRI would eliminate the need for extra equipment, and provide a consistent methodology for monitoring and reporting swallowing compliance. Also, it would allow covert monitoring of natural swallows.

In this investigation an interleaved fMRI/dynamic MRI sequence (SimulScan) with joint acquisition of the cortical, subcortical and oropharyngeal systems was developed. This results in effectively simultaneous acquisition of fMRI/dynamic MRI data, as the repetition time is similar to existing approaches, and functional images are captured at a rate adequate for resolving the functional (BOLD fMRI) signal. The sequence was previously described in (19). The sequence eliminates the need for extra monitoring equipment, and provides a consistent methodology for monitoring and reporting swallowing compliance. SimulScan builds upon fast FLASH spiral sequences to provide interleaved acquisition, while maintaining dynamic imaging rates of 14.5 frames per second. The sequence uses a spiral *k*-space trajectory for which susceptibility changes result in blurring. Breaking the spiral-design into multiple shots can minimize this blurring artifact to levels that do not interfere with interpretation of the motion (13).

The SimulScan sequence is applied to covertly monitor natural (uncued) swallows. The covert swallowing task was chosen to provide a more precise evaluation of sensorimotor components related to swallowing and to limit ancillary functional activation caused in visual or auditory stimulation that results from cued tasks. Additionally, the natural swallow is shown to have small accompanying motions, limiting motion-related artifacts in the functional imaging results. The aim of this research was to test the feasibility of using SimulScan to effectively image oropharyngeal structures and functional brain activation during swallowing. The designed pulse sequence is described and a protocol is given describing the acquisition and analysis. Additionally, functional activations from the covert swallowing task are compared to a previously published cued fMRI swallowing task.

MATERIALS AND METHODS

All data were acquired on a Siemens Magnetom Allegra 3 T head-only scanner equipped with a single channel birdcage head coil. The scanner is capable of a per axis maximum gradient amplitude of 40 mT/m, and slew rates up to 400 mT/m/ms, although limits of 34 mT/m and 250 mT/m/ms were used in this work. The developed pulse sequence that interleaves the functional and dynamic acquisitions, SimulScan, was used to collect the data. Three healthy young adult volunteer subjects with no history of swallowing disorders were studied in accordance with the protocol approved by the institutional review board of the University of Illinois.

SimulScan Pulse Sequence Design

The SimulScan pulse sequence consists of interleaved dynamic and fMRI acquisition blocks as shown in Fig. 1a. A single mid-sagittal slice was used to capture dynamic oropharyngeal swallowing events and 24 oblique axial slices were used to acquire functional slices of the brain. The sequence acquired 1 dynamic image for every functional slice, as shown in Fig. 1b. Both the dynamic and functional portions of the acquisition used a spiral acquisition (20). The dynamic acquisition involved a 6-shot spiral-out FLASH acquisition to image a single 6 mm thick mid-sagittal slice. The parameters used include 240×240 mm FOV, 96×96 matrix, 2.5×2.5 mm resolution, TE 1.1 ms, flip angle of 10° and a TR of 68.8 ms. The resulting dynamic frame rate was 14.5 frames per second. The fMRI acquisition used a single-shot spiral-in readout to image 24 slices each 4 mm thick, 240×240 mm FOV, 64×64 matrix, 3.75×3.75 mm resolution, TE 25 ms, flip angle of 80° and an effective TR of 1.6512 s.

Task Paradigm

To investigate brain activations associated with natural spontaneous swallowing, a simple covert-swallowing paradigm was employed. The focus of the experiment was not explained to the subject until after the scans were completed. Padding was used in the head coil to restrict subject head motion. Three 15-min scans were acquired while the subject watched an animated film of their choice. The film was not associated with the swallowing task. The task varies from traditional fMRI paradigms where a stimulus is provided to cue the task. Instead this study examined uncued swallows. Because swallowing occurs naturally, the imaging sequence was simply made long enough to ensure enough swallows would be observed. Previous research suggested that the subjects would swallow at an average rate of 1.32 spontaneous swallows/minute (21). This would result in ~ 60 swallows over the study with random spacing determined by the subject. The onsets of swallowing events were later determined using the acquired dynamic images of the oropharyngeal region. In addition to the SimulScan sequence, high-resolution proton density and T2 weighted images were acquired with the functional

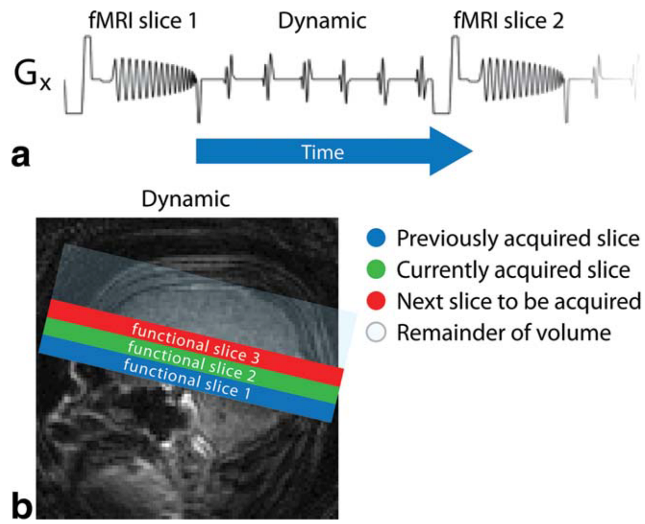

FIG. 1. Illustration of (**a**) gradient in *x*-direction, G_x, during SimulScan, showing interleaved sequence blocks (**b**) relative position of dynamic acquisition and functional slice acquisitions.

acquisition slice prescription in addition to a high-resolution 3D structural image using a magnetization-prepared rapid acquisition of gradient echo sequence.

Data Analysis

Data analysis consisted of four steps: determining the timing of swallow onsets, fMRI analysis, quantifying the contribution of motion, and identifying regions of activation. To determine swallow onsets, a rectangular region of interest (ROI) was placed on the sagittal dynamic image in the area including the base of tongue and the posterior pharyngeal wall (oropharynx). The ROI was positioned so that contact between the base of the tongue and the oropharynx during swallowing would fall within the ROI and the average intensity within the region would increase (Fig. 2a). The peak intensities were a robust indicator of swallowing activity (Fig. 2b), and were similar to timings gathered by visual inspection of the dynamic videos. The detection method required the ROI be small enough so that the intensity increase caused by contact of the base of the tongue to the oropharynx would cause a detectable change in the mean intensity of the ROI, but large enough so that movement variability would not cause the contact point to move outside of the ROI. A ROI of 10 voxels was used. To quantify detection capabilities, the SNR of this signal was found by analyzing the amplitude of the ROI time-series during a swallow versus its baseline standard deviation. The SNR of the swallowing peaks is 18.1, showing that the swallowing events were easy to detect from the time series data. For comparison, a visual inspection of the contact between the base of the tongue and the oropharynx was also used as an indicator of swallowing. The automated timings were used in the subsequent fMRI analysis.

Functional MRI data processing was performed using the fMRI Expert Analysis Tool from the FMRIB's Software Library (22). Pre-statistics processing steps include motion correction using MCFLIRT (23) and brain extraction using BET (24). A gaussian kernel was used to smooth using a FWHM of 5.0 mm and a high pass filter of 30 s was applied to the time series of functional MRI data. The computed onset timings were convolved with the canonical hemodynamic response function for use in general linear modeling for each run of each subject. A multistage registration and normalization was then performed using the low-resolution T2 image and the high-resolution magnetization-prepared rapid acquisition of gradient echo sequence, to match the MNI template. A second-level fixed effects analysis was performed to find the activations of each subject over all runs. And a second higher-level fixed effects analysis was performed to find activation common among all subjects. This was thresholded with a *Z* threshold of 3.0 and Cluster P threshold of 0.05 to correct for multiple comparisons with gaussian random field theory (25). Anatomical regions of activation were determined by comparing thresholded functional maps to the Talairach atlas provided in FSL (26).

RESULTS

Image Quality

The dynamic anatomical images show susceptibility related artifacts. In general these artifacts are not ideal, but the resulting images are sufficient to detect the

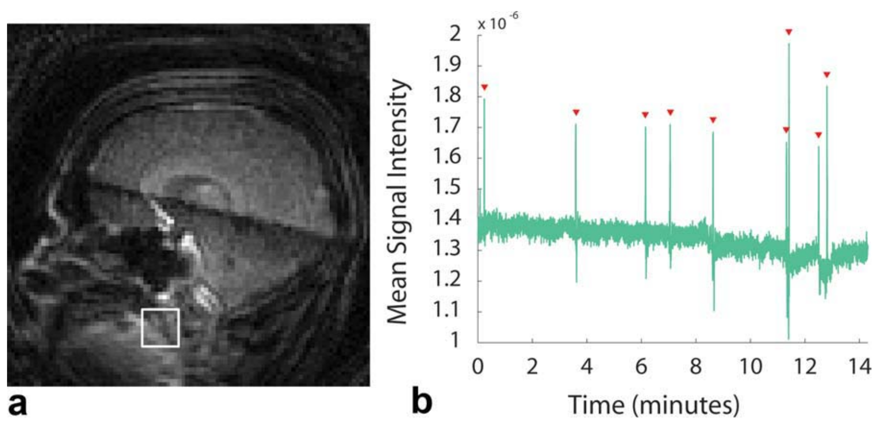

FIG. 2. Illustration of ROI analysis used for automated detection of swallowing, (**a**) ROI is positioned to cover base of the tongue and posterior pharyngeal wall, (**b**) detected swallows, indicated by marking above peaks.

Table 1
Number of Uncued Swallowed Detected for Each Subject

	Subject 1	Subject 2	Subject 3
Run 1	9	35	30
Run 2	6	36	14
Run 3	11	42	12
Average	8.67	37.67	18.67

swallowing motion. Also, both dynamic and functional images show a saturation effect due to the interleaved acquisition. For example, a sagittal dynamic slice will have a saturated band at its intersection with an axial functional slice that was acquired just prior to the dynamic slice (Fig. 2a). The axial functional slices also have a saturated band caused by the sagittal dynamic slice.

Number of Swallows

Timings onsets of the swallows were determined from the ROI analysis based on the dynamic images as described in "data analysis" and in Fig. 2b. Subjects 1, 2, and 3 swallowed on average 8.67, 37.67, and 18.67 times per run (Table 1). Subject 2 had a higher swallowing frequency. Notably this subject reported to have flu-like symptoms on the day of the experiment, which may be associated to the more frequent swallows.

Functional Brain Activation and Validation

Results of fMRI data processing show significant activations in sensorimotor regions of the brain (Fig. 3). As can be observed, activation was significant in most of the primary motor and somatosensory cortex, as well as in sensorimotor integration areas, such as the thalamus and premotor cortex.

To validate the functional results detected and to examine how a natural swallow compares to a cued swallow, results of the present experiment were compared to a previous fMRI investigation using a cued swallowing paradigm (2). Table 2 shows the comparison of regions that were found as activated in these two studies. The results show that nearly all of the same areas related to motor control, sensory input and somatosensory integration are significantly activated, although the significant activations from this study are much more localized to motor control areas.

Motion Analysis

Motion determined by MCFLIRT ranged from 0.04169 mm to 1.0992 mm for translational displacement and 0.0017 rad to 0.0118 rad for rotation among all subjects. The max displacement and rotational motion for subject 1 was 1.0992 mm and 0.0101 rad. Subject 2 showed max translational motion of 0.8664 mm and max rotational motion of 0.0118 rad. Subject 3 showed translation and rotational motion of 0.9639 mm and 0.0100 rad. Although these movements are sub-voxel in size and should cause minimal error in the functional results, if the motion is correlated with the swallows it can provide false activation results. To examine the impact of motion on the fMRI results, we examined activations with and without motion parameters included as regressors in the general linear model. Activations were compared from the two analyses and showed the same areas of activation in each case with similar z-scores in activated regions. Further, no correlated gross head motion was observed with visual inspection of the dynamic images of the natural swallows.

DISCUSSION AND CONCLUSION

The objective of this work was to develop and validate a pulse sequence capable of simultaneous functional brain imaging and dynamic imaging of the biomechanics of natural oropharyngeal swallows. The results support the feasibility and applicability of the SimulScan technique. All swallowing events for all subjects were successfully detected by automated processing of the dynamic MRI acquisition. Functional MRI, simultaneously acquired, was used to find areas of significant brain activations in regions typically identified as components of the swallowing network. These functional results were validated through comparison to previously published results, showing many of the same areas of activation. To our knowledge, this is the first study documenting simultaneous acquisition of functional MRI and dynamic MRI of swallowing. Apart from improving understanding of the neural control of normal healthy swallowing, this new technique will enable simultaneous visualization of neural and muscular components of swallowing abnormalities in patients with dysphagia, and thus allow direct clinical associations between the two components.

The fMRI results showed significant activation in regions commonly identified as swallowing network areas, as shown in previous studies (2). The differences between the two studies, including Brodmann area 8, Brodmann area 41, precuneus (Table 2), and visual areas, may be explained by many factors. The precuneus for instance is known to be associated with visual and tactile cuing (27). The additional areas of activation seen during swallowing in the previous cued water

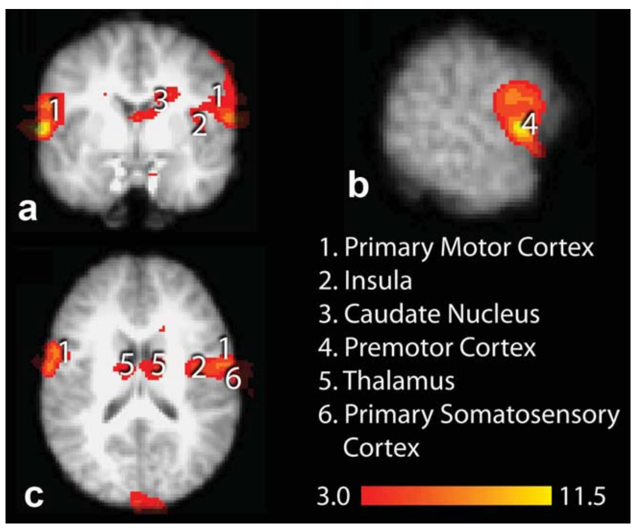

FIG. 3. Results of functional analysis in (**a**) coronal, (**b**) sagittal, and (**c**) axial cross-sections.

Table 2
Areas of Significant Activation During Uncued Swallowing Found in This Study Compared to a Previous Study of Cued Water Swallowing

Research Study	Common to this Study and Cued Water Swallowing (2)	Cued Water Swallowing (2) Only
Areas of activation during swallowing	Primary motor area (precentral gyrus, BA 4)	
	Primary sensory area (postcentral gyrus, BA 3)	
	Supplementary motor area and middle and superior frontal gyrus (BAs 6 and 9)	BA 8 of frontal cortex
	Insular cortex (BA 13)	
	Heschl's gyri (BA 42)	Heschl's gyri (BA 41)
	Superior and inferior parietal lobules	
	Anterior and posterior cingulated gyrus (BAs 24, 30, 31)	
	Thalamus	
	Midbrain	
	Cuneus	Precuneus
	Cerebellar regions in both the anterior and posterior lobes	
Visual areas		Extensive Visual processing areas

swallowing study may be due to visual processing of the stimulus and additional sensory input in the oral cavity caused by the entrance and presence of the water. It is likely that this study using SimulScan was able to show the activations related to natural spontaneous swallowing without interference of external oral sensory and visual stimuli. Note that while the present study is natural in the sense that it was not cued, it was performed in a supine orientation. Typical MRI scanners constrain the subject to a supine orientation during imaging. Studies have shown that gravity can have effects on the behavior of muscles involved in speech (11). Swallowing performed in an upright MR scanner may provide images of swallowing free of these gravity driven effects.

In this research, the dynamic MR images acquired by SimulScan can be used to determine swallowing initiation times, but more sophisticated dynamic information is available in these images. Dynamic MR images can provide more detail of soft tissue structures involved in deglutition than video fluoroscopy, without need for a contrast agent. In future work, oropharyngeal structures could be identified and more clinically relevant movement parameters could be measured. Note that although this study shows the monitoring of a mid-sagittal slice during swallowing, the sequence allows separate graphical slice prescriptions for the dynamic and functional imaging portions of the sequence. The dynamic slice prescription can be modified to image clinically relevant parameters in any plane for improved monitoring of specific swallowing parameters.

Given that SimulScan achieves imaging rates of 14.5 frames per second, it is not fast enough to fully resolve certain swallowing phenomena such as velar elevation during swallowing that is achieved in approximately 50 ms (17). Higher frame rates are necessary to delineate these motions and the current study can only resolve the endpoints of the motion (13). Since swallows are repeated many times to obtain adequate signal-to-noise from the functional MRI activations, retrospective gating could be used to obtain a higher-quality, average dynamic image of the motion involved (9,28). High frame rates have been achieved in MRI by gating the acquisition. Gated acquisitions do not account for potentially significant variations that can result from something as simple as repeating a single word (9,13). The current study relies on a real-time monitoring of the dynamic events, i.e., ungated acquisitions. However, these images suffer from several significant tradeoffs: spatial vs temporal resolution and temporal resolution vs magnetic susceptibility artifacts. Additional work on optimizing the acquisition and reconstruction may improve some of the current tradeoffs.

A major concern when imaging swallows is motion-induced artifacts. Functional images may be distorted by bulk movement inside the field of view, as well as movement outside the field of view, such as swallowing. Problems may include steady-state signal errors or changes in magnetic susceptibility artifacts (29). To limit motion-induced activation artifacts, some cued swallowing studies use the behavioral interleaved gradient method (30–32). That method has not been employed here. Instead, statistical analysis was performed with and without motion parameters included in the regression model to examine the impact on the functional results from motion during natural swallows. Bulk translational and rotational motions were determined by MCFLIRT (23). Also sagittal dynamic images were observed to examine the extent of bulk motion. No visible motion-induced artifacts are present in this analysis, either in the functional images or bulk motion in the dynamic images, which suggests that natural saliva swallows are associated with minor movements.

Besides bulk motion artifacts, which were shown to be minimal, it is possible that variations in the magnetic field in the human brain result from the process of swallowing. The magnetic susceptibility depends on the orientation of tissue structures with air spaces throughout the head and neck. Motion of the oropharyngeal structures, especially the tongue and jaw, alter the susceptibility-induced magnetic field distribution even at the brain slices being imaged for the fMRI component of the SimulScan sequence. Although not seen in the current data set, artifactual activations could occur in data at or near the base of the brain due to these motion-induced susceptibility changes. Simultaneous field-mapping could be added to the sequence by introducing a slight delay to the data readouts during the dynamic imaging portion of the sequence (33). This would result in obtaining dynamic field map values in the sagittal plane through the brain to monitor changes associated with movements. The penalty for this addition to the sequence would be an increase in the effective TR for both the dynamic and functional portions of the SimulScan sequence.

The proposed technique may prove an essential presurgical tool for patients who have to undergo neurosurgery for brain abnormalities and occasionally end up with multiple swallowing difficulties post surgery. This technique may offer important information on individualized neural areas that should be spared during surgery for an intact swallow to occur post surgery. Furthermore, this simultaneous imaging possibility provides the innovative capability to apply and visualize the effects of swallowing treatment techniques (such as head postural adjustments or sensory enhancement techniques) on the oropharyngeal biomechanics and the brain activation at the same time. This has the potential to significantly enhance understanding of the direct effects of swallowing treatments on the oropharyngeal swallowing and on the neural control of swallowing. This may lead to improvement of existing treatment techniques and development of new, individualized and more effective treatment techniques.

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