NeuroMix—A single-scan brain exam

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Abstract
Purpose: Implement a fast, motion-robust pulse sequence that acquires $T_1$-weighted, $T_2$-weighted, $T_2$*-weighted, $T_2$ fluid-attenuated inversion recovery, and DWI data in one run with only one prescription and one prescan.

Methods: A software framework was developed that configures and runs several sequences in one main sequence. Based on that framework, the NeuroMix sequence was implemented, containing motion robust single-shot sequences using EPI and fast spin echo (FSE) readouts (without EPI distortions). Optional multishot sequences that provide better contrast, higher resolution, or isotropic resolution could also be run within the NeuroMix sequence. An optimized acquisition order was implemented that minimizes times where no data is acquired.

Results: NeuroMix is customizable and takes between 1:20 and 4 min for a full brain scan. A comparison with the predecessor EPIMix revealed significant improvements for $T_2$-weighted and $T_2$ fluid-attenuated inversion recovery, while taking only 8 s longer for a similar configuration. The optional contrasts were less motion robust but offered a significant increase in quality, detail, and contrast. Initial clinical scans on 1 pediatric and 1 adult patient showed encouraging image quality.

Conclusion: The single-shot FSE readouts for $T_2$-weighted and $T_2$ fluid-attenuated inversion recovery and the optional multishot FSE and 3D-EPI contrasts significantly increased diagnostic value compared with EPIMix, allowing NeuroMix to be considered as a standalone brain MRI application.

Keywords
brain, fast MRI, multicontrast, neuroimaging, screening
1 | INTRODUCTION

In contrast to CT, the acquisition of a single MRI contrast can take several minutes, and a whole MRI exam often takes tens of minutes. Long scan times can cause patient discomfort, which occasionally leads to premature termination of an exam. Moreover, the probability of motion artifacts tends to increase with both the acquisition time of each contrast as well as the duration of the entire scan. Consequently, for uncooperative patients, or for time-critical situations such as stroke or head trauma, CT is usually the preferred option—despite the ionizing radiation being particularly unwanted for pediatric patients due to the long-term cancer risks. The alternative of sedating an uncooperative patient for an MRI examination is typically accompanied by a significant organizational effort, high costs, and long wait times.

Consequently, shortening scan times and increasing motion robustness have been long-lasting endeavors since the early days of MRI. Improved gradient hardware has reduced scan times substantially and is now largely limited by peripheral nerve stimulation thresholds. On the acquisition side, parallel imaging and compressed sensing marked significant breakthroughs to cut down the scan time. Moreover, motion-robust sampling strategies have been developed, most importantly self-navigated techniques, such as PROPELLER, which has been widely adopted in the field, but also other non-Cartesian sampling strategies like radial sampling or stack of stars.

Another approach is single-shot Cartesian imaging, such as single-shot EPI or single-shot fast spin echo (SSFSE), in which the temporal footprint of a single slice is short enough to freeze the motion in most cases.

A comprehensive clinical brain MRI scan includes several contrasts such as T1-weighted (T1w), T2-weighted (T2w) and T2*-weighted (T2*w), T2 fluid-attenuated inversion recovery (T2-FLAIR), and DWI, each playing a part in determining the diagnosis. For example, T1w provides excellent gray matter–to–white matter contrast; white-matter hyperintensities can be easily depicted using T2w and T2-FLAIR weighting; T2*w is very sensitive to bleeding; and DWI highlights restricted diffusion of water molecules, which plays a key role in stroke assessment.

For many pathologies, such as trauma, stroke, edema, inflammation, or hemorrhages, this list of contrasts is sufficient.

With the actual sampling time getting shorter due to advancements in hardware, acquisition and reconstruction, non–acquisition time becomes increasingly important to monitor. This non–acquisition time includes slice planning, sequence download time, and prescan/tuning time. This also includes dummy cycles to prepare a certain magnetization state and wait times for the longitudinal magnetization to recover. Much of this dead time could be avoided if several contrasts were acquired in a single scan. One option is synthetic MRI, in which the conventional MRI contrasts are synthesized in the reconstruction through parametric mapping. A disadvantage of synthetic MRI is the oversimplification of the underlying model, which fails to capture the complexity of the tissue resulting in differences between the synthetic and the conventional contrasts. In addition, the T2*w and DWI contrasts are usually not included in these models. Alternatively, all of the desired contrasts can be acquired in a fast and efficient way by combining the conventional acquisitions into one sequence. Recently, we presented EPIMix, in which we combined a single-shot EPI readout with different magnetization preparations, yielding a highly motion-robust sequence acquiring the top-five contrasts T1w, T2w, T2-FLAIR, T2*w, and DWI in a little bit more than a minute. Several clinical studies have acknowledged that the quality of EPIMix is sufficient with only marginally lower diagnostic performance compared with conventional imaging. The main clinical drawback for EPIMix was the inherent geometric distortions caused by the EPI readout, which makes diagnosis near the skull base particularly problematic. The EPIMix method was therefore not sufficient to use as the only scan of a brain MRI screening protocol.

In this work, we present a new, generalized, multicontrast framework called NeuroMix (to emphasize brain applications, not solely using EPI readouts), which encompasses the following:

- An additional software top-level layer to KS Foundation that further modularizes the programming code to create and run an MRI sequence such that the acquisition of several contrasts can be set up with minimal programming effort.
- T1w, T2w, T2-FLAIR, T2*w, and DWI contrasts acquired with single-shot sequences to maintain the motion robustness of EPIMix, but the two most important contrasts for clinical neuroimaging (T2w and T2-FLAIR) are acquired without EPI distortions using a SSFSE readout.
- Optional additional acquisitions are added: isotropic T1w 3D-EPI, SWI 3D-EPI, and a high-resolution multishot T2w fast spin echo (FSE).

With the addition of FSE contrasts and optional high-resolution acquisitions, we envision NeuroMix to be used as a standalone single-scan brain MRI exam for screening. We describe the acquisition order of each contrast and the corresponding slices to minimize the time when no data are acquired. The performance of NeuroMix is compared against its predecessor, EPIMix, as well as conventional MRI contrasts for clinical neuroimaging.
imaging. Finally, we show early clinical results on a pediatric and an adult patient.

2 | METHODS

2.1 | Programming framework

NeuroMix, as well as its predecessor EPIMix, was programmed for GE Healthcare MRI systems using the vendor-provided programming SDK EPIC together with an abstraction layer called KS Foundation, which is publicly available (www.ksfoundationepic.org). The multilayered programming structure of NeuroMix is overviewed in Figure 1, starting with the lowest-level EPIC at the bottom, where specific instructions in the waveform memory are created. This propagates up to the highest level, “ksneuromix.e,” which for the most part is a collection of desired sequence parameters, or sequence recipes. In EPIMix, all layers above the KS Foundation abstraction layer were collapsed into one. In that setting, it was challenging to optimize each specific contrast individually, such as changing the readout from EPI to FSE, or from 2D to 3D. Moreover, changing specific properties of the slice stack, such as orientation and slice thickness, on a per-contrast basis was not possible. Therefore, all of the layers above the KS Foundation layer were implemented for this work to enable NeuroMix. In the “sequence-independent design” layer, we share functionality such as slice orientation, slice acquisition order, TR computations including specific absorption rate (SAR), and gradient heating or k-space properties such as resolution, and phase-encoding plans. The “sequence generator” layer uses the capabilities of all underlying layers to create and serve an MRI sequence to the top layer, including timing calculations and waveform generations, but also real-time execution such as slice looping and data tagging. As of now, we have implemented FSE and EPI sequence generators, in which only EPI has 3D capability. Importantly, the sequence generator layer takes care of inversion preparation as well as including the generation of the inversion sequence and timing computation, linking the main sequence (in our case EPI or FSE) to the inversion sequence, and playing both jointly in real time. Finally, in the top layer, “ksneuromix.e,” all contrasts are designed to be completely self-contained, with no direct dependence on the user interface, using a recipe-like list of input arguments such as TE, TI, TR, FOV, and matrix sizes, but also slice prescription or saturation bands. Crucially, only the top layer is connected to the user interface. Moreover, the user interface has been restricted to only allow the selection of the FOV, number of slices, optional contrasts, and number of averages.

**FIGURE 1** The layered programming structure of NeuroMix starts with the vendor-provided EPIC SDK at the bottom and “ksneuromix.e” as the top sequence layer. All layers above KS Foundation have been implemented for this work.
This allowed us to optimize NeuroMix for the use case of brain scanning without exposing the complexity of those optimizations, which will be described later, to the user. Some examples of how NeuroMix is structured at a
programmed level are given in Supporting Information Figure S1.

### 2.2 Pulse sequences

The waveforms of all subsequences played in NeuroMix are depicted in Figure 2, and all corresponding default sequence parameters are overviewed in Table 1. NeuroMix uses four single-shot 2D-EPI sequences, including an inversion-prepared T1w sequence (T1-FLAIR EPI; Figure 2D), a T2*w gradient echo (T2*w EPI; Figure 2F), a fully sampled, sequential low flip gradient echo (FLEET EPI; Figure 2E) for parallel imaging calibration and a diffusion-weighted spin echo (DW EPI; Figure 2C). Moreover, NeuroMix accommodates a T2w SSFSE (Figure 2H) and an inversion-prepared T2w single-shot FSE (T2-FLAIR SSFSE; Figure 2I). These single-shot sequences belong to the motion-robust core of NeuroMix, where we expect usable images even under severe head motion, similar to EPIMix.\(^{23}\) Optionally, the end user can also include a high-resolution multishot FSE (T2w FSE; Figure 2G) in the NeuroMix scan with almost half the voxel size of T2w SSFSE. All FSE sequences used a linear phase-encoding order, where the refocusing flip angle of all FSEs is modulated using the TRAPS technique.\(^{31}\) Finally, NeuroMix consists of two optional 3D-EPI sequences: a sagittal T1w 3D-EPI (Figure 2B) with isotropic voxels to enable slice reformatting in any plane; and SWI 3D-EPI (Figure 2A) with higher in-plane resolution.

The FOV coverage and acquisition order for each contrast is depicted in Figure 3A. NeuroMix is prescribed in the axial scan plane with frequency-encoding direction left-right (Figure 3A, green box), with slices typically aligned with the anterior commissure–posterior commissure line. Importantly, the end user only prescribes a square FOV for the slice stack of the 2D-EPI sequences. For the SSFSE and FSE sequences involved, NeuroMix swaps the phase/frequency encoding directions and reduces the left–right (phase-encoding) FOV to 75%. Furthermore, the resolution in the slice direction is doubled for SWI 3D-EPI, and an inferior saturation band is automatically added to suppress in-flow artifacts. Finally, the scan plane of T1w 3D-EPI is automatically rotated from the axial to the sagittal plane, and the left–right FOV is reduced to 75%, similar to the FSE sequences. In this way, the frequency-encoding direction of T1w 3D-EPI is turned into the superior–inferior direction, which helps to suppress flow...
|                  | T1w 3D-EPI | SWI 3D-EPI | EPIMix T1-FLAIR | EPIMix FLEET | EPIMix T2* | EPIMix T2w/DWI | EPIMix T2-FLAIR |
|------------------|------------|------------|----------------|--------------|------------|----------------|----------------|
| Sagittal         | Axial      | Axial      | Axial          | Axial        | Axial      | Axial          | Axial          |
| 7.4 ms           | 23.8 ms    | 17.0 ms    | 11.3 ms        | 20.5/36.2 ms | 45.8/102.3 ms | 100.3/119.8 ms |
| 17 ms            | 52 ms      | 1300 ms    | 42.5 ms        | 930/1220 ms  | 2410 ms    | 5500 ms        |
|                  | –          | –          | 600 ms         | –            | –          | –              | 2750 ms        |
| 168/192          | 312/312    | 108/180    | 120/180        | 108/180; 180/180 | 120/180; 120/180 |
| 240 × 240 mm²    | 240 × 240 mm² | 240 × 240 mm² | 240 × 240 mm² | 240 × 240 mm² |
| 192 × 192        | 312 × 312  | 180 × 180  | 180 × 180      | 180 × 180    |
| 1.2 × 1.2 mm²    | 0.8 × 0.8 mm²  | 1.3 × 1.3 mm²  | 1.3 × 1.3 mm²  | 1.3 × 1.3 mm² |
| 152              | 84         | 36         | 36             | 36           |
| 1.2 mm           | 2.0 mm     | 4.0 mm     | 4.0 mm         | 4.0 mm       |
|                  | 22°        | 17°        | 5°             | 18°          |
| 24               | 12         | 1          | 3              | 1            |
| 3                | 2          | 3          | 3              | 3            |
| 8                | 8          | –          | –              | –            |
| 1424/59 µs       | 1576/131 µs | 800/267 µs  | 800/267 µs     | 800/267 µs   |
| 7                | 26         | 36         | 36             | 40/60        |
| 16.31 mT/m       | 24.32 mT/m | 34.58 mT/m | 34.58 mT/m     | 34.58 mT/m   |
| 3                | 5          | 1          | 0              | 0            |
| 22.5 s           | 28.3 s     | 18.5 s     | 9.8 s          | 4.1 s        |

Artifacts. Moreover, we can use a non-slice-selective water excitation pulse for improved gray matter/white matter contrast stemming from reduced magnetization-transfer effects. 29

Designing the acquisition order of NeuroMix is a delicate process, particularly the challenge of avoiding unnecessary wait times for magnetization recovery. The two 3D sequences are acquired in steady state, and few dummy TRs are needed because the acquisition starts with the high frequencies of k-space. Thereafter, the DWI-EPI sequence is played, which necessarily requires one dummy TR for accurate apparent diffusion coefficient (ADC) values. The user also has the option to acquire an additional b = 0 volume with opposite blip polarity for distortion correction purposes. 32 In addition, the dummy TRs of T1w 3D-EPI, SWI 3D-EPI, and DWI EPI are used to acquire Nyquist ghost-correction data, in which the data of DWI EPI are used for all other 2D-EPI sequences.

Inversion-prepared contrasts benefit from thicker slices of the inversion sequence compared with the main imaging sequence to compensate for slice profile imperfections and CSF inflow. Inflow can cause false hyperintense signals, especially in T2-FLAIR, which could mimic or obscure pathology. Therefore, we have chosen to double the inversion slice thickness and to acquire T1-FLAIR EPI and T2-FLAIR SSFSE in two passes, where one pass covers the odd (slice groups A + C in Figure 3A) and one the even slices (slice groups A + C in Figure 3A).

After the DWI-EPI block, the first pass of T1-FLAIR EPI is played, including one dummy TR. Thereafter, FLEET EPI and T2*w EPI data are acquired without dummy TRs. Note that due to the low flip angles of FLEET EPI and T2*w EPI, the impact on the longitudinal magnetization is small. Moreover, during FLEET EPI, the magnetization can recover just enough for a reasonably attenuated signal of CSF in the T2*w EPI. If the user has chosen to acquire an additional b = 0 volume with opposite blip polarity, an additional FLEET volume with the same blip polarity is acquired after T2*w EPI to avoid ghosting due to distortion mismatch of the calibration data and the undersampled data.

A T2-FLAIR sequence consists of an inversion block and the main readout block, separated by the TI. For the following, we refer to them combined as a T2-FLAIR block. For the default parameter choices (Table 1), two T2-FLAIR blocks are needed to accommodate all slices of
one pass. The crucial challenge, however, was to achieve a homogenous CSF suppression across the slice stack for T2-FLAIR. We assign all slices of a T2-FLAIR block to a group, resulting altogether in four slice groups: A to D (Figure 3A).

For T2w SSFSE, we change from odd to even slices and play slice group D, which contains fairly well-recovered magnetization, only saturated by the widened inversion pulse of the T1-FLAIR EPI sequence. Next, T2-FLAIR SSFSE is played for slice group B, which was also last saturated by the inversion of T1-FLAIR EPI. Next, the second T2-FLAIR block of the first pass is played on slice group D, which was last saturated by the T2w SSFSE sequence. Finally, T2w SSFSE is acquired for slice group B, in which the magnetization has had time to recover during the T2-FLAIR block. The reasoning behind this slice order is that the time between T1-FLAIR EPI and the first T2-FLAIR block on slice group B is approximately the same as the time between T2w SSFSE on group D and the second T2-FLAIR block on slice group D. Consequently, the magnetization state of the two T2-FLAIR blocks is similar. We found the corresponding TI that achieves homogeneous suppression of the CSF to be 2900 ms. The corresponding TI was adjusted to 3050 ms. For the interested reader, an audio file of NeuroMix running the default protocol (Table 1) is provided in Supporting Information Audio S1.

The optional multishot T2w FSE is played on all slice groups at the end of the second pass. Magnitude inconsistencies between the first and all subsequent shots are problematic, especially for CSF due to the long T1 relaxation. Two mitigation options were explored in this work: a dummy TR and second an incoherent sampling scheme to disperse the formation of visible artifacts due to shot-to-shot magnitude differences.

In this work, EPIMix and conventional imaging protocols are used as references. The imaging parameters of EPIMix are also provided in Table 1. For EPIMix, all contrasts were acquired in two passes. Moreover, EPIMix acquired dual EPI readouts for the T2w/DWI and T2-FLAIR contrasts to improve SNR. More details of the EPIMix implementation can be found in Skare et al. and Sprenger et al. At 3T, SAR needs to be taken into account for rapid FSE sequences, resulting in additional dead time after each sequence playout to limit the average SAR. The SAR limits are defined in most countries by the International Electrotechnical Commission, defining maximum values for 6-min-average and 10-s-average SAR, the latter which shall not be higher than twice of the former. In this work, the TRAPS technique was used to reduce the SAR of the FSE sequences. Moreover, we took advantage of the fact that the durations of all subsequences are known from the beginning and are significantly shorter than 6 min. Consequently, each sequence (contrast) is evaluated with twice the SAR budget than normal, by obeying only the 10-s-average SAR limit. Thereafter, all sequences of NeuroMix were jointly evaluated against the 6-min-average SAR limit, resulting in no SAR-related dead time at 3 T. Figure 3B depicts moving averages of the squared Bi of a complete NeuroMix sequence run, indicating the relative SAR levels of the different subsequences.

All imaging was performed on a 3T MR system (Signa Premier; GE Healthcare, Milwaukee, WI) using a 48-channel head coil from the same vendor. In vivo data were acquired on 2 volunteers and 2 patients in accordance with the institutional review board policy, and informed consent was obtained. The movement of the head of the pediatric patient was recorded using a markerless motion tracker (Tracoline TCL3.1m; research version provided by TracInnovations, Ballerup, Denmark), but no prospective updates of the slices were performed.

2.3 | Reconstruction

The image reconstruction was implemented in MATLAB (MathWorks, Natick, MA) using a vendor-provided SDK called Orchestra. Linear Nyquist ghost correction was applied to all EPI data using the calibration lines acquired in the dummy TRs of SWI 3D-EPI, T1w EPI, and DWI EPI, in which the latter was also used for all 2D-EPI sequences. This was followed by ramp sampling correction of the EPI data to Cartesian coordinates in the frequency-encoding direction. Parallel imaging reconstruction was performed for the 2D-EPI contrasts using GRAPPA with FLEET EPI as a motion robust external calibration. All other contrasts included autocalibration lines, and the parallel imaging reconstruction was done using autocalibrating reconstruction for Cartesian imaging. When applicable, partial Fourier reconstruction was done using projection onto convex sets. For the coil combination, sum of squares was used, except for SWI EPI, in which adaptive coil combine was used. Intracontrast 2D motion correction was done using a rigid model for T1-FLAIR EPI and an affine
model for DW EPI, which also corrected for the zero-order and linear eddy currents induced by the diffusion gradients. The diffusion processing included averaging of all \( b = 0 \) volumes and all DWI volumes, and their log ratio was used to compute the isotropic ADC. The vessel contrast of SWI 3D-EPI was improved using SWI processing, combining magnitude and phase.\(^{38}\) The extra \( b = 0 \) volume with reverse blip polarity was reconstructed to later allow for distortion correction of all 2D-EPI contrasts.\(^ {32}\) However, in favor of increased motion robustness and shorter image-reconstruction time, distortion correction was not enabled in the clinical NeuroMix reconstruction pipeline, nor for the volunteer experiments. However, distortion correction of existing NeuroMix data at a later point will enable a better voxel-wise multicontrast analysis.

3 | RESULTS

Figure 4 compares all EPIMix contrasts (Figure 4A) with the corresponding single-shot contrasts of NeuroMix. For a fair comparison, and contrary to Table 1, NeuroMix was acquired without optional contrasts, with four diffusion directions (tetrahedral) and no reverse polarity volumes, resulting in an overall scan duration of 1:20 min for NeuroMix versus 1:12 min for EPIMix. Unsurprisingly, the biggest differences can be appreciated for the T2w and T2-FLAIR contrasts, in which NeuroMix uses an SSFSE instead of an EPI readout. Although the EPIMix T2-FLAIR sequence provided slightly stronger contrasts, SSFSE T2-FLAIR significantly outperformed EPIMix in terms of image sharpness, SNR, and absence of geometric distortions. The T2w-SSFSE sequence was acquired with 1-mm in-plane resolution compared with 1.3 mm for EPIMix (Table 1), resulting in a clear sharpness gain and an improved gray matter/white matter delineation. The other three contrasts (T1-FLAIR, DWI, and T2*w) are very similar. The only obvious difference is the increased SNR in NeuroMix T2*w compared with EPIMix T2*w due to the higher flip angle used. For the interested reader, we provide a set of dicoms including all contrasts of NeuroMix and EPIMix in Supporting Information Data S1.

Figure 5A,B compares the CSF suppression in T2-FLAIR SSFSE of a conventional slice order with the optimized slice order described in Figure 3A. Conventional slice order means that T2w SSFSE is played on all odd slices, and thereafter T2-FLAIR SSFSE is played on all even slices (or vice versa for the next pass). Note that for this
experiment, contrary to Table 1, the number of slices was reduced to 32 to achieve shorter TIs while still allowing all slices in each pass to fit in two T2-FLAIR blocks. Despite testing a range of TIs, no homogenous CSF suppression across the slices could be achieved with the conventional slice order, because the longitudinal magnetization before the first and the second T2-FLAIR block is in different states (Figure 5A). Nevertheless, the optimized slice order results in homogenous CSF suppression at about TI = 2900 ms (Figure 5B). Figure 5C depicts four consecutive slices of T2-FLAIR SSFSE slices for the default 4-mm protocol (Table 1) with 36 slices (two T2-FLAIR blocks per pass) and a 3-mm protocol with 48 slices (three T2-FLAIR blocks per pass), both with excellent CSF suppression.

Figure 6 illustrates the impact of the number of averages on T1-FLAIR EPI and DW EPI. Although the default protocol only consists of five T1-FLAIR EPI averages, the user can choose up to 20 averages, significantly improving the SNR (Figure 6A). The same holds for DWI EPI, in which an increase in the number of directions notably increases the delineation of, for example, the substantia nigra and the red nuclei (arrows in Figure 6B).

Another way to customize NeuroMix are the optional contrasts T1w 3D-EPI, SWI 3D-EPI, and T2w FSE. Figure 7A depicts selected T1w 3D-EPI images in the acquired sagittal plane as well as axial and coronal reformats. The biggest advantage of T1w 3D-EPI, besides reformatting possibilities, is the about 5 times reduction in geometric distortions compared with T1-FLAIR EPI (Table 1). The shorter echo-train length (Table 1) also results in improved image sharpness compared with T1-FLAIR EPI (Figure 4B). Figure 7B shows a dramatic improvement of SWI 3D-EPI in terms of resolution and vessel contrast compared with T2*w EPI (Figure 4B). Finally, Figure 7C compares T2w SSFSE with the high-resolution multishot T2w FSE, revealing, as expected, a noticeable increase in detail. Figure 7D demonstrates that the incoherent FSE sampling scheme for T2w FSE yields ghost-free images without a dummy TR, saving about 9 s of scan time.

The last two figures give an impression of the performance of NeuroMix in a clinical setting. Figure 8 compares our clinical imaging brain-tumor protocol with EPIMix and NeuroMix’s default protocol. The post-op tumor patient was a 78-year-old female radiated for anaplastic xanthoastrocytoma with a right temporal lobe resection cavity, dural contrast-enhancing residual tumor, and radiotherapy-related gliosis in surrounding white matter. The two diffusion contrasts, isotropic DWI and isotropic ADC, appear similar across the conventional protocol, EPIMix, and NeuroMix. The conventional diffusion acquisition exhibits better SNR and slightly lower distortions due to multiplexed sensitivity encoding, which is also reflected in the scan time. On the other hand, EPIMix and NeuroMix provide sharper diffusion-weighted images.
due to less filtering in the reconstruction. The use of two $b = 0$ volumes for NeuroMix results in an improved isotropic ADC SNR compared with EPIMix. Figure 8B illustrates the lack of distortion artifacts from the temporal bone on clinical T2w and T2w SSFSE compared with disturbing artifacts on EPIMix T2w EPI. For the same slice, a substantial reduction of geometric distortions for T1w 3D-EPI compared with T1-FLAIR EPI can be appreciated in Figure 8C, where the contrast-enhancing dural residual tumor can not be delineated on T1-FLAIR EPI (arrows, Figure 8C). Figure 8D shows a similar delineation of high-signal gliosis on all T2-FLAIR images. Small signal dropouts from metallic craniofix can be seen on the clinical T2-FLAIR and NeuroMix T2-FLAIR SSFSE, while EPIMix’s T2-FLAIR EPI shows significant distortions and signal pileup in those regions (arrows, Figure 8D). Figure 8E illustrates a better delineation of low signal vascular structures on SWI 3D-EPI (a developmental venous anomaly in the left parietal lobe marked with an arrow) compared with the T2*w EPI (having lower resolution).

Figure 9 depicts a NeuroMix scan (default settings) on a 7-year-old pediatric patient in whom no pathology was found. The patient’s head motion was recorded using the markerless optical tracking system, and the corresponding motion plots are shown in Figure 9A. Of the 7 pediatric patients scanned, the exam presented here had among the highest amount of head motion. The SWI data had some minor high-frequency artifacts from nodding motion. For the 3D T1w acquisition, the level of motion was low and picked up again for some of the 2D contrasts. The T2-FLAIR SSFSE had a few slices with insufficient CSF suppression due to out-of-plane motion (Supporting Information Figure S2). Yet, despite up to 10° of head rotation during the NeuroMix scan, the contrasts of NeuroMix were generally diagnostic despite T2-FLAIR contrast corruption of some slices.

4 | DISCUSSION

In this work, we presented a new multicontrast sequence, NeuroMix, that includes the five most important contrasts for neuroimaging; T1w, T2w, T2*w, T2-FLAIR, and DWI. Based on clinical experience from several hospitals with its predecessor, EPIMix, NeuroMix has been developed as a standalone screening tool for brain MRI. Most importantly, the EPI readouts traditionally suffering from geometric distortions due to the low phase-encoding...
bandwidth were replaced by SSFSE readouts for the contrasts considered crucial for neurological screening: T2w and T2-FLAIR. Furthermore, three optional contrasts were introduced: high-resolution SWI 3D-EPI, isotropic T1w 3D-EPI, and high-resolution multishot T2w FSE. Finally, a flexible number of averages for T1-FLAIR and DWI was made available to the end user. In the shortest configuration, NeuroMix takes only 1:20 min for full brain coverage with 4-mm slice thickness (Figure 4), which is only 8 s more than EPIMix and can be attributed to the use of SSFSE readouts. With all three of the optional contrasts enabled and using the maximum of 20 averages for DWI and T1-FLAIR, the scan time increases up to 4 min.

A strength of NeuroMix is its customizability. For example, the neuroradiologists at the Karolinska University Hospital have chosen a default protocol (Figures 8 and 9 and Table 1) that takes 2:28 min, including all single-shot sequences, T1w 3D-EPI, and SWI 3D-EPI.

NeuroMix is prescribed in the user interface of the scanner as a single sequence, only allowing the end user to select the number of slices, the slice thickness, make moderate changes to the FOV, and choose which optional sequences to play as well as the number of averages for each contrast. The simple and fast prescription makes NeuroMix a more attractive screening tool that requires less-experienced staff at all times of the day. We have already seen that one of the strengths of EPIMix was consistency both over time and across hospitals.

Only one prescan is required, and the acquisition of all calibration data such as parallel imaging and Nyquist ghost calibration is integrated with the data acquisition. Moreover, some NeuroMix contrasts such as T2*w EPI, FLEET EPI, T2w SSFSE, T2-FLAIR SSFSE, and T2w FSE are acquired in a transient state without preparing a longitudinal magnetization steady state. To achieve this, a new slice-ordering scheme for T2w SSFSE and T2-FLAIR SSFSE was implemented (Figure 3A) to enforce a more homogenous CSF suppression in the T2-FLAIR SSFSE images without adding additional dead time (Figure 5) for T2-FLAIR. For comparison, a naive implementation of the NeuroMix core, where all contrasts that are acquired in a transient (except for FLEET EPI) include one dummy TR (per pass), would be 40.6 s longer. An incoherent k-sampling scheme was used to suppress ghosting artifacts due to shot-to-shot longitudinal magnetization inconsistency, which enabled the acquisition of T2w FSE without a dummy TR (Figure 7), saving an additional 9 s of scan time.

With the sequence code for EPIMix, we were not able to extend beyond 2D-EPI readouts or, for example, enable flexible per-contrast slice prescriptions. Therefore, we first needed to implement an extension of the KS Foundation programming framework for MRI pulse programming on GE Healthcare MRI scanners. This extension included a sequence generator layer (Figure 1) to easily set up and run multiple sequences within one main sequence.
We consider this step a crucial prerequisite for a multi-contrast sequence like NeuroMix, in which a top-layer main sequence merely requests subsequences through short design recipes. Each contrast can be optimized independently, with its stack of slices, resolution, FOV orientation, or phase encoding plans. This also makes complex slice acquisition ordering as shown for T2-FLAIR SSFSE (Figure 3A) and flexible SAR evaluation for short-term peak SAR and average SAR (Figure 3B) possible.

Acquiring all contrasts in one main sequence has its advantages and disadvantages. On the one hand, it enables us to optimize the data acquisition for a specific purpose, in our case neuroimaging of the brain, and to take maximal advantage of the system’s hardware. To cover the full brain, 36 slices with 4-mm thickness were considered sufficient, and all parameters were optimized for that case, such as the echo train length of T2-FLAIR SSFSE to fit all slices in two T2-FLAIR blocks per pass. The user can choose any number of slices, but this may create additional dead time. For example, in case of more slices an additional T2-FLAIR block is needed and in case of less slices deadtime is added to T1-FLAIR to achieve a minimum TR for SNR reasons. The disadvantage of this approach is that the optimization has to be done for each hardware setup separately. It will be the subject of future work to optimize NeuroMix for lower-tier MR systems and other field strengths. Thanks to the layered, inert, programming structure used by NeuroMix, those optimizations will be limited to hardware-specific changes of the design recipes, rather than complex programming changes.

The work on the NeuroMix sequence will continue, and there are more promising techniques that could be envisioned for future versions. NeuroMix uses conventional k-space sampling schemes with moderate parallel imaging factors of two or three (Table 1), where the image resolution of each contrast in NeuroMix (Table 1) is a careful compromise among SNR, scan time, and sequence timing. There are several interesting techniques...
that can help to further increase the image resolution and quality without adding scan time, such as joint reconstruction or the use of deep learning, for example, to denoise the complex images or to improve reconstruction performance. Moreover, T1-FLAIR EPI still suffers from geometrical distortions, while the optional 3D T1w exhibits dramatically reduced distortions but is not motion robust. Each of these T1w sequences takes just over 20 s to acquire, but ideally one would like to get the best of both. Therefore, one of our highest priorities is replacing the steady-state EPI readout of T1-FLAIR with another readout technique without EPI distortions but preserve the very short temporal footprint for motion-robustness purposes. Possible candidates are another SSFSE, in which increased SAR and reduced T1w contrast due to the long readout are the major concerns. The latter problem could also be taken care of by using a PROPELLER acquisition. This, however, would result in longer scan times. An alternative option is a snapshot 2D-MPRAGE readout, which has proven to be very motion robust. Regarding the T2* contrast, sequential multishot 2D-EPI is a promising technique to reduce distortions and increase the resolution while preserving the motion robustness. Simultaneous multislice could also be considered, as it has been shown to improve the efficiency of 2D sequences. Although the SSFSE readouts would likely run into SAR limits, simultaneous multislice is suitable to increase the scan efficiency of T2w FSE. Moreover, with wave controlled aliasing in parallel imaging, an extremely fast 3D acquisition technique has recently been presented. This could be used as an alternative to T1w 3D-EPI, but also

FIGURE 8 Comparison of the clinical imaging brain-tumor protocol following gadolinium with EPI/Mx and NeuroMix's default protocol. (A) DWI, clinical multiplexed sensitivity encoding (MUSE) with four shots per direction and voxel size 1.25 × 1.25 × 4 mm³. (B) T2w, clinical T2w PROPELLER with voxel size 0.75 × 0.75 × 4 mm³. (C) T1w, clinical T1w-FLAIR 3D-FSE with voxel size 1 × 1 × 1 mm³. The contrast-enhancing dural residual tumor is marked with an arrow. (D) T2-FLAIR, clinical T2-FLAIR 3D-FSE with 1 × 1 × 1 mm³. Image artifacts from metallic craniofix are marked with an arrow. (E) T2* with no clinical reference acquired. Signal voids are caused by metallic craniofix. A developmental venous anomaly in the left parietal lobe is marked with an arrow.
add additional contrast options for T2-FLAIR, in which 3D acquisitions are generally superior in terms of CSF inflow and image contrast.\textsuperscript{50} Finally, MRA is an important contrast, not the least for early stroke assessment,\textsuperscript{51} and is currently missing in NeuroMix.

With T1-FLAIR EPI, T2w SSFSE, T2*w EPI, T2-FLAIR SSFSE, and DWI EPI, all five main contrasts are acquired with single-shot readouts and therefore usually yield sharp images even in the presence of head motion (Figure 9). The optional multishot sequences T1w 3D-EPI, SWI 3D-EPI, and T2w FSE offer better contrast, higher resolution, or isotropic resolution, but are also more vulnerable to motion artifacts such as ghosting. In NeuroMix, the single-shot contrasts can always serve as a backup to the optional contrasts, resulting in a very high probability that NeuroMix will create a set of images that is sufficient for a diagnosis. Unfortunately, in the case of large out-of-plane head motion, an inconsistent magnetization history can corrupt the image contrast even for the single-shot sequences. Inversion-prepared sequences such as T1-FLAIR or T2-FLAIR\textsuperscript{23,45} are especially sensitive. It will be part of future work to also include prospective motion correction into NeuroMix to further improve its robustness.

5 | CONCLUSIONS
We have presented a new multicontrast sequence, NeuroMix, which acquires T1w, T2w, T2-FLAIR, T2*w,
and DWI contrasts in a single scan, requiring only one prescription and one prescan. A new programming framework was implemented to allow different sequences to be isolated from each other and then combined in a lightweight, top-level main sequence. Motion-robust single-shot EPI and FSE sequences are combined with optional multishot sequences that provide higher resolution, better contrast, or the possibility to reformat. This results in a scan time range of 1:20 min (pure single shot) to 4 min (all optional sequences and averages) for full brain coverage. NeuroMix enables a fast and motion-robust single-scan brain exam, allowing higher patient throughput with less discomfort and possibly less need for sedation.

CONFLICT OF INTEREST
Tim Sprenger is an employee of GE Healthcare.

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Tim Sprenger receives salary from GE healthcare.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

**FIGURE S1** Programming structure of the top three layers of the NeuroMix framework

**FIGURE S2** Further details of the pediatric patient scan in Figure 9. Apart from sharp images in the native scan plan axial, coronal reformatals are depicted to show the severity of motion. Also, failed CSF suppression can be observed in some slices due to motion between the inversion pulse and the imaging sequence. As a comparison, a heavily motion-corrupted conventional 3D spoiled gradient echo is shown that was acquired in 2:30 min at a later time of the exam

**SUPPORTING INFORMATION DATA S1** The ZIP file contains a dicom data set including all contrasts of NeuroMix and EPIMix

**AUDIO S1** Audio file of NeuroMix running the default protocol (Table 1)

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