Multiparametric imaging with heterogeneous radiofrequency fields

Martijn A. Cloos\textsuperscript{1}, Florian Knoll\textsuperscript{1}, Tiejun Zhao\textsuperscript{1,2}, Kai T. Block\textsuperscript{1}, Mary Bruno\textsuperscript{1}, Graham C. Wiggins\textsuperscript{1} & Daniel K. Sodickson\textsuperscript{1}

Magnetic resonance imaging (MRI) has become an unrivalled medical diagnostic technique able to map tissue anatomy and physiology non-invasively. MRI measurements are meticulously engineered to control experimental conditions across the sample. However, residual radiofrequency (RF) field inhomogeneities are often unavoidable, leading to artefacts that degrade the diagnostic and scientific value of the images. Here we show that, paradoxically, these artefacts can be eliminated by deliberately interweaving freely varying heterogeneous RF fields into a magnetic resonance fingerprinting data-acquisition process. Observations made based on simulations are experimentally confirmed at 7 Tesla (T), and the clinical implications of this new paradigm are illustrated with \textit{in vivo} measurements near an orthopaedic implant at 3T. These results show that it is possible to perform quantitative multiparametric imaging with heterogeneous RF fields, and to liberate MRI from the traditional struggle for control over the RF field uniformity.
During the last four decades, magnetic resonance imaging (MRI) has evolved into a pre-eminent clinical imaging modality and invaluable research tool. Much of this development proceeded through increasingly advanced mechanisms to subdue experimental imperfections within the magnetic resonance (MR) scanner. MR systems now deploy ever-more-elaborate calibration \(^1\)\(^-\)\(^4\) and compensation mechanisms\(^5\)\(^-\)\(^10\) in pursuit of an elusive balance between image quality and scan time. Nevertheless, most clinical MR examinations have noticeable imperfections, and experienced radiologists are called upon to see through the subtle distortions produced by suboptimal conditions\(^11\)\(^-\)\(^14\). One notable source of imperfections is inevitable spatial variations in the radiofrequency (RF) fields used to excite and detect the MR signal.

Far from being a new problem, non-uniform RF fields have posed a challenge since the inception of MRI. Applied RF fields (known as \(B_1^+\) fields) illuminate the subject and determine the ‘exposure’ of the image\(^3\). A non-uniform exposure can result in undesirable artefacts that shade the field of view and obfuscate important details in the image\(^11\)\(^-\)\(^14\). Attempts to overcome these artefacts generally strive to harness \(B_1^+\) to best approach a uniform exposure. However, subject-specific electrodynamic interactions between the incident RF field and patient anatomy preclude the construction of a tractable general-purpose uniform \(B_1^+\) source\(^11\)\(^-\)\(^13\). Instead, a large body coil built into the bore of the scanner is often used to approximate an even illumination\(^16\),\(^17\). Residual imperfections are then mitigated using dedicated compensation techniques such as adiabatic pulses\(^9\), whose efficacy is limited by safety constraints on RF energy deposition into tissue, as well as by unwanted relaxation and magnetization transfer effects\(^18\).

Alternatively, more complex techniques, such as parallel transmission with multiple RF sources, can be employed to tailor the net illumination to the subject\(^6\),\(^7\). However, such tailored solutions require meticulous calibration measurements\(^1\)\(^-\)\(^4\) and elaborate inline calculations\(^6\),\(^7\),\(^19\),\(^20\) that impede workflow and lengthen examination time\(^20\),\(^21\).

Here we eliminate the need for a uniform \(B_1^+\) field, adiabatic pulses, dedicated calibration measurements and subject-specific calculations with a solution we call ‘Plug-and-Play MR fingerprinting’ (PnP-MRF). Like other techniques before it, the MRF approach was originally developed and applied in the traditional context of a precisely calibrated and uniform \(B_1^+\) field\(^2\). PnP-MRF liberates MRF from these constraints and enables accurate quantitative imaging free of RF-related artefacts. At the same time, PnP-MRF extracts the actual \(B_1^+\) fields experienced by the imaged body from the measurement data. This self-calibrating nature of our method marks a clear departure from the traditional paradigm of calibration and control in MRI, and enables use of the method without fine-tuning, that is, in a ‘plug-and-play’ mode, over a broad range of experimental conditions.

**Results and Discussion**

**The impact of \(B_1^+\) non-uniformities on MRF.** MRF measurements are designed to probe the dynamics of a spin system as it is perturbed by a sequence of RF and gradient pulses. Instead of encoding individually intelligible images, MRF seeks to capture the time evolution of the net magnetization in each voxel as it evolves throughout the sequence. When the \(B_1^+\) field is perfectly uniform, each of these signal evolutions, referred to as fingerprints, can be matched uniquely to one entry of a simulation-based dictionary, which identifies underlying tissue properties, including relative proton spin density (PD), longitudinal relaxation time (T1) and transverse relaxation time (T2).

However, MR systems seldom produce a uniform \(B_1^+\) field. The top row in Fig. 1 shows the simulated \(B_1^+\) field distributions produced by an idealized 16-rung bore-sized transmit coil at different frequencies. Even at the lower end of the clinical spectrum (1.5 T, 64 MHz), where the RF wavelength is still larger than the axial cross-section of the average human torso, there are noticeable spatial variations in the \(B_1^+\) field. Although the

![Figure 1](Image)

**Figure 1 | The performance of the conventional MRF framework at different field strengths.** Each sub-figure shows the same axial slice through the abdomen. The top row shows simulated \(B_1^+\) field distributions produced by a bore-sized circularly polarized RF body coil at three different proton Larmor frequencies associated with 1.5 T (64 MHz), 3.0 T (128 MHz) and 7.0 T (298 MHz) MR scanners. The left-most reference case assumed a (physically infeasible) fully uniform \(B_1^+\) field. The CV of the \(B_1^+\) field amplitudes was 0, 6, 24 and 39%, for the reference, 64, 128 and 298 MHz cases, respectively. The next three rows show the PD, T1 and T2 maps reconstructed from a synthetic MRF measurement at each field strength, juxtaposed to the ground truth maps (left column) used as inputs to the simulation (based on assignment of representative parameter values for distinct tissue types in each segmented image). For simplicity of comparison, the T1 and T2 values were kept constant with field strength. Note the progressive deviation from ground truth with increasing frequency.
coefficient of variation (CV) of the $|B_{1+}|$ field is only 7%, this variation already biases the T2 and PD maps measured using MRF (Fig. 1, column 2).

As the frequency is increased from 64 to 128 MHz (3.0 T), the RF wavelength becomes comparable to the abdominal cross-section, which gives rise to strong $B_{1+}$ depressions in the anterior and posterior areas of the body (Fig. 1, column 3). This characteristic $B_{1+}$ distribution (CV = 24%), often observed at 3.0 T (refs 11,12), further degrades the PD and T2 maps to the point where some of the T2 values measured in the right kidney exceed the scale set by the maximum values included in the ground truth simulation.

At 298 MHz (7.0 T), the RF wavelength is reduced to ~15 cm, which causes the aforementioned $B_{1+}$ depressions to extend into so-called $B_{1+}$ voids (CV = 39%), that is, areas that do not experience any RF excitation (Fig. 1, column 4). In the absence of any appreciable $B_{1+}$, even adiabatic pulses, such as the one at the start of the conventional MRF sequence22, fail to yield reliable inversions (Supplementary Fig. 1). As a result, in addition to strong distortions in the T2 and PD maps, the reconstructed T1 map now also shows strong artefacts (Fig. 1, column 4).

Multiparametric imaging with heterogeneous RF fields. While it has been shown that a dedicated23 or integrated24 $B_{1+}$ calibration can be used to correct mild $B_{1+}$ distortions in MRF measurements, it is impossible to extract a viable signal from areas devoid of RF field. MR fingerprints originating from such regions are signal-starved and governed by small-tip-angle excitations, which limits the signal encoding to the linear domain of the Bloch equations25. As a result, the MR fingerprints belonging to different tissues become indistinguishable (Fig. 2).

One strategy to mitigate such signal voids is $B_{1+}$ shimming, which strives to create a desirable $B_{1+}$ distribution in the subject by driving multiple independent RF sources in parallel. The above-mentioned body coil, for example, can be broken up into 16 azimuthally distributed dipole elements, which allows the field non-uniformity to be reduced from a CV of 39% to a CV of 23% at 298 MHz (Fig. 3a). Although this is a substantial improvement, it is simply impossible to create a truly uniform $B_{1+}$ field with a finite number of RF sources13. Owing to the short RF wavelength in human tissue, an interference pattern forms, which often leads to residual $B_{1+}$ voids in the abdomen (Fig. 3b) and artefacts appear in the derived multiparametric maps (Fig. 4, centre column).

Prior-MRF circumvents these problems by co-encoding the $B_{1+}$ distribution into the MR fingerprints. This way, the effect of spatial variations in the $B_{1+}$ fields can be separated out and quantified alongside tissue parameters of interest, in one comprehensive image reconstruction process. Moreover, Prior-MRF enables multiple complementary RF configurations to be interwoven into the sequence, which circumvents the usual pitched battle against $B_{1+}$ voids.

Instead of trying to calibrate out all $B_{1+}$ voids, a ‘plug-and-play’ solution can be constructed by interweaving two or more distinct coil modes into the MRF framework. Even though the exact $B_{1+}$ distributions are not known a priori, different coil configurations tend to have distinct features. The CP mode (a bright centre surrounded by a halo of $B_{1+}$ voids) and the Gradient mode (which contains a RF void in the centre surrounded by areas with relatively high $B_{1+}$) of a coil array (Fig. 3c), for example, have been noted to be largely complementary26. Experimentally, approximations of these modes can be identified in less than 10 s by first aligning the MR signal phases in a central region of the subject to obtain the approximate CP mode from which the approximate gradient mode can be derived based on the azimuthal angle of the coil elements. Moreover, once the system has been characterized, these coil modes can be hardcoded into the sequence for future use.

Although each of these approximate coil modes produces a heterogeneous $B_{1+}$ field (CV 41% and 38%, respectively), a viable MR fingerprint is obtained from all regions in the field of view because the $B_{1+}$ voids do not overlap (Fig. 3d). This makes it possible to reconstruct artefact-free multiparametric maps throughout the abdomen at 7.0 T (Fig. 4, right column).

This new paradigm of interweaving multiple heterogeneous RF fields has the potential to overturn the fundamental design considerations governing transmit coils in MRI. Instead of striving to realize coil configurations that minimize RF field imperfections, the focus can be shifted towards designs that provide two or more complementary illuminations. This is an inherently easier problem to tackle because, in our approach, RF pulses are played out in an interleaved manner and the illuminations do not directly interact with one another. Thus, in contrast to tailored field configurations in traditional MRI techniques ($B_{1+}$ shimming15 or parallel RF transmission6,7), here the destructive interference between RF sources is completely avoided. Importantly, such an approach also avoids the constructive interference of electric fields that could cause local heating of conductive tissues27,28 and does not require energetic refocusing or adiabatic pulses. In other words, our approach addresses the two greatest hurdles for widespread adoption of multicoil transmission: safety and workflow.

Experimental comparison at 7 T. The same wavelength effects that complicate abdominal imaging can also be observed in smaller samples with a high relative permittivity. A water phantom at 7 T, for example, also gives rise to extremely heterogeneous $B_{1+}$ fields. The top row in Fig. 5 shows the experimental results obtained with the MRF method in a 16.5 cm diameter phantom at 7 T (CV of the $B_{1+}$ is 39%). Similar to the numerical experiments shown above (Fig. 1), the T1 map remains accurate in most places except for those areas where the $B_{1+}$ is extremely low and the adiabatic condition of the preparation
The B1⁺ field distributions at 7 T and corresponding MR fingerprints. The same three regions of interest are marked in each B1⁺ map. Each region of interest falls in a distinct B1⁺ void in one of the maps. (a) The B1⁺ distribution obtained in the abdomen after RF shimming with 16 azimuthally distributed dipoles (CV = 23%). (b) The first 480 time points of the MR fingerprint measured in the three different regions of interest resulting from excitation with the RF-shimmed B1⁺ distribution. The fingerprint in the region of the B1⁺ void (3) is signal-starved and notably less distinctive than the other two fingerprints (obtained from regions 1 and 2). (c) The B1⁺ distribution of the approximate CP mode obtained by aligning the MR signal phases in the centre of the abdomen and the approximate gradient mode derived by incrementing the RF phase according to the azimuthal angle of the coil element (CV = 41% and 38%, respectively). (d) The first 480 time points of the PnP-MRF fingerprint measured in the three different regions of interest resulting from interleaved excitations using the two coil modes. Since the B1⁺ nulks for the two modes do not overlap, all regions experience substantial excitation at regular intervals during the PnP-MRF sequence, and all three fingerprints retain high signal and distinctiveness.

Figure 5 | Experimental results obtained at 7 T. The top row shows the multiparametric maps (PD, T1 and T2) obtained with the conventional MRF sequence. The bottom row shows the multiparametric maps (PD, T1, T2 and B1⁺) obtained with our PnP-MRF approach. The asterisk indicates that no receive sensitivity correction was applied. All subfigures show the same axial slice through a 16 cm diameter cylindrical phantom.

The B1⁺ -shimmred MRF versus PnP-MRF. The left-hand column shows the ground truth abdominal PD, T1 and T2 maps. The middle column shows tissue property maps reconstructed from a synthetic 16-channel B1⁺-shimmed conventional MRF experiment at 7 T. The right-hand column shows tissue property maps reconstructed from a synthetic PnP-MRF experiment interweaving the approximate CP and gradient mode at 7 T. Each row of figures is plotted with the same scale. Whereas residual B1⁺ variation in the shimmed case results in substantial artefacts (particularly in the T2 and PD maps, but also in selected regions of the T1 map—for example, in the right kidney), the PnP-MRF case shows no systematic deviation from ground truth.

pulse cannot be fulfilled. The T2 map, on the other hand, is biased throughout the slice except for the central area where the B1⁺ amplitude best approximates the nominal flip-angle for which the sequence was designed.

The bottom row in Fig. 5 shows the multiparametric maps measured using PnP-MRF. Analogous to the PnP-MRF simulations shown in Fig. 4, we first obtained the approximate CP mode by aligning the phases in the centre of the phantom and derived the approximate gradient mode based on the azimuthal angle of the coil elements. This pre-scan adjustment can be performed in 7 s with little or no impact on the workflow. Moreover, this calibration only needs to be performed once for each coil and can then be hardcoded into the PnP sequence.

Even though the B1⁺ distributions produced by these same coil modes look fundamentally different from those in the abdomen (Fig. 4c versus Fig. 5), the fields produced by these two coil configurations remain complementary. Interwoven into the PnP-MRF sequence these two coil modes circumvent persistent RF voids, which enables the accurate quantification of PD, T1, T2 and B1⁺ throughout the slice.

Currently, B1⁺ maps are not used in routine clinical imaging. Nevertheless, these maps capture the complex interactions between the subject anatomy and the incident RF field. The opportunity to rapidly quantify the RF field could be an asset for electrical property tomography, an MR technique that aims to recover dielectric tissue property distributions based on the local curvature of B1⁺ (refs 29,30). In turn, these dielectric maps could provide a new set of complementary parameters (tissue conductivity and permittivity) to aid in the diagnostic process31,32.

Instead of the simultaneous estimation of B1⁺ fields and tissue properties shown here, one could envision the use of dedicated traditional B1⁺ calibration scans as prior information for PnP-MRF. Although prior knowledge of the B1⁺ field distribution would help to constrain the cross-section of the dictionary that needs to be considered during the reconstruction process, any inaccuracies in these external B1⁺ maps will propagate into the T1 and T2 maps. Considering that most traditional B1⁺ mapping techniques are only accurate within a relatively limited range of B1⁺ values, residual artefacts may be expected when imaging with highly heterogeneous RF fields (Supplementary Note 1 and Supplementary Fig. 2). Moreover, external B1⁺ calibration scans are prone to misregistration artefacts because of subject motion,
and they require additional scan time that increases the duration of the comprehensive examination.

**Imaging near orthopaedic implants.** The previous experiments focused on the feasibility of quantitative imaging at ultrahigh field strength (7 T, 289 MHz)—an area that remains highly challenging despite many years of research and optimization using traditional paradigms. This, however, is just one example out of a large body of documented cases describing subject-specific RF field interactions that lead to severe artefacts in MR\(^1\)–\(^5\),\(^\ddagger\)–\(^2\),\(^\ddagger\)–\(^3\),\(^\ddagger\)–\(^6\). Orthopaedic implants, such as the titanium rod depicted in Fig. 6a, for instance, interact strongly with the incident RF field, leading to significant \(B_1^+\) artefacts at clinical field strengths\(^4\)–\(^6\).

To demonstrate the feasibility of our PnP-MRF approach in a clinically relevant setting, we implemented it on a whole-body 3 T (128 MHz) MRI system (Skyra timTX, Siemens, Erlangen, Germany), in which the built-in transmit coil can be decomposed into two linear components (L1 and L2). We used this setup either (a) to drive both linear components simultaneously with a fixed amplitude and phase relationship to produce an elliptically polarized (EP)-mode (a two channel \(B_1^+\) shim) optimized for the anatomy under investigation\(^7\) or (b) to interleave the two linear components one after the other into the PnP-MRF sequence.

The appearance of \(B_1^+\) artefacts depends on the level of \(B_1^+\) non-uniformity as well as on the imaging sequence selected. Clinical MR examinations primarily use turbo spin echo (TSE)-based sequences especially near implants because of their high signal-to-noise ratio, their flexible contrast weighting and the IR-TSE parameters used here produce a relatively bland contrast, affecting the opposing leg are also removed (Fig. 6b vs c). The RF-related inhomogeneities no longer overshadow the bone marrow and muscle tissues reconstructed in situations where traditional contrast-weighted MR techniques struggle (Fig. 6e,f). Shading due to RF variations become a problem, which could be addressed by switching to a three-dimensional (3D) image-encoding strategy.

In some less-challenging cases, a single inhomogeneous RF field may suffice to perform a PnP-MRF measurement. For example, in the absence of an orthopaedic implant, the exposure produced in the legs by the CP or EP mode, although heterogeneous, is often free of \(B_1^+\) voids (Supplementary Fig. 4). In such cases, either of these modes may serve as a single heterogeneous field source, since interleaved illumination by L1 and L2 is no longer required to ensure adequate exposure in all regions of interest (ROI). As in the multi-illumination implementation described above, the non-uniform \(B_1^+\) distribution produced by such a source is distilled from the measurement data, leaving a complete set of unbiased multiparametric maps without need for additional calibration.

Besides heterogeneous \(B_1^+\) fields, main magnetic field variations are another long-standing problem in MR. It has already been shown that MRF is relatively robust against such field variations\(^2\)–\(^4\),\(^\ddagger\)–\(^6\). Nonetheless, in extreme cases, e.g., near stainless steel implants as opposed to the titanium implant shown here, additional work may be necessary to avoid residual artefacts. In particular, deformation of the excitation slice profile may become a problem, which could be addressed by switching to a three-dimensional (3D) image-encoding strategy.

One other noteworthy observation is the lack of contrast in the PD map obtained with our PnP-MRF method (Fig. 6c). Contrary to many clinical PD-weighted imaging protocols (see, for example, Supplementary Fig. 3), our PD map suggests

---

**Figure 6 | Conventional MRI versus PnP-MRF in the presence of an orthopaedic implant.** (a) X-ray image showing the orthopaedic implant. (b) Contrast-weighted axial image through the legs obtained using a conventional inversion recovery (IR) TSE sequence. Signal voids appear both in the vicinity of the implant and in the contralateral leg. (c–f) Quantitative maps obtained using PnP-MRF, including PD, \(B_1^+\), \(T1\) and \(T2\), respectively. Units are arbitrary for PD (c), micro Tesla for \(B_1^+\) (d), seconds for \(T1\) (e) and milliseconds for \(T2\) (f). (g) Enlargements, extracted from b (red frame) and c (green frame), comparing the region surrounding the implant with conventional (left) and PnP-MRF (right) approaches. (PnP-MRF scan time: ~28 s per slice.) Note the absence of \(B_1^+\)-related signal voids in any of the PnP-MRF parameter maps.
that the total number of protons per unit of volume is similar in adipose and muscle tissues (Supplementary Note 2 and Supplementary Fig. 5). Specialized MR techniques such as (refs 35,36) and mass spectrometry data indeed support the notion that adipose and muscle tissues have a comparable proton density (see Supplementary Note 3). However, hidden beneath this bland PD map lies another contrast-rich landscape that can be accessed by incorporating the Dixon fast-water separation method35 into the PnP-MRF framework (Supplementary Note 4).

Validation. Quantitative results from in vivo measurements in relation to literature values are summarized in Supplementary Table 1. To further validate PnP-MRF, phantom measurements were compared against a clinically prohibitive 5.5-h gold-standard measurement (maps not shown). In all cases, a high degree of correspondence may be noted between PnP-MRF measurements and time-consuming dedicated gold-standard measurements. (Supplementary Fig. 6).

However, with current proof-of-principle implementation, it still remains difficult to measure extremely long T2 values in areas with a low signal-to-noise ratio. This can be understood by looking at the sequence design (Supplementary Fig. 7). Currently, the RF pulse train is segmented into groups of 120 excitations (cumulative duration ≈600 ms), which limits the ability to differentiate fingerprints with a very long T2. The adipose tissue in Fig. 6f, for example, shows some T2 variability that may be related to the multieponential relaxation of the fat in combination with variations in the signal-to-noise ratio. Longer RF train segments could help make fingerprints with a long T2 more distinct, thereby reducing the sensitivity to noise.

In addition to the tissue-dependent parameters T1 and T2, we also validated the $B_1^+$ distributions (CV = 15 and 16% for the first and second transmit channels, respectively). Results of a dedicated saturation-based RF field mapping calibration measurement (total scan time 3 min 50 s per slice)3 were compared with the $B_1^+$ maps recovered during the PnP-MRF reconstruction process (Fig. 7b). This test confirmed that our approach indeed extracts the correct $B_1^+$ contributions from the measurement (correlation factors exceed 0.96 at all acceleration factors). In other words, PnP-MRF exhibits a self-calibrating property that allows quantitative MR imaging with highly non-uniform RF fields.

One important asset of MRF is its efficiency, that is, the ability to rapidly quantify multiple tissue properties at once. Table 1 lists the scan time per slice from two prominent publications on MRF,
justuxtaposed to our PnP-MRF experiments. Although PnP-MRF simultaneously quantifies $B_1^+$ in addition to the tissue properties, the relative efficiency remains comparable, especially considering that the times listed for conventional MRF do not include the time that might be required for a separate $B_1^+$ calibration measurement (at least in the cases of mild heterogeneity for between separate scans, and provides a natural mechanism to PnP-MRF avoids potential problems related to misregistration joint encoding of tissue properties and $B_1^+$ heterogeneities for robust encoding of information.

In a sense, although it departs from long-standing conventions of MR image acquisition, the PnP-MRF approach to embracing rather than controlling inhomogeneities represents a natural extension of the fundamental principles upon which MRI was first founded. In their seminal 1973 articles, Lauterbur and Mansfield and Grannell showed that high-resolution images could be created using induced local interactions with heterogeneous magnetic fields—fields that might otherwise have been viewed as imperfections in traditional MR experiments. Their disruptive invention, however, still required that the image-encoding fields be known in advance. In the current work, we have demonstrated a means of self-discovering, from a single suitably encoded data stream, diverse and accurate information not only about the imaged body but also about the conditions under which images have been generated. Although the method described here is specific to MRI, it is based on a broad underlying fundamental concept of treating heterogeneities in the experimental conditions as a source of information rather than as a generator of artefacts, and leveraging complementary heterogeneities for robust encoding of information.

**Methods**

**Sequence design.** The design space for MRF sequences is quite broad, given the large number of variations of parameters and delays involved. In the absence of an analytic sequence optimization process, we designed a proof-of-principle sequence. The PnP-MRF sequence consists of four segments, each containing 120 excitations separated from one another by a 4.8–8 ms interval (Supplementary Fig. 7). The first and third segments contain spoiled gradient echoes, which alternate, from one echo to the next, between two orthogonal coil configurations. (In general, an arbitrary number of complementary RF coils or coil configurations may be used.) These RF-spoiled excitations combine the cumulative effects of both RF coil configurations into a complex spin evolution and predominantly serve to encode $B_1^+$ and $T_1$. The other segments, with $\theta$=150° RF phase cycling and spoiling gradients, allow stimulated echoes to form, adding a $T_2$ relaxation component into the mix. Collectively, these 480 excitations (4 segments × 120 per segment) capture a distinct signal evolution. This signal evolution acts like a ‘fingerprint’, which is used to identify the underlying tissue properties.

In addition to a spatially varying $B_1^+$ amplitude, each excitation also has its own spatially varying phase distribution (defined as the argument of the complex $B_1^+$ field). Because the relative phase between excitations contains no clinical information, we designed the sequence such that the relative $B_1^+$ phase distributions are not entangled with the spin dynamics. In the first and third segments, the phase distribution produced by the preceding excitation is removed by de-phasing the transverse magnetization with a combination of gradient and RF spoiling. The other segments, however, need to partially refocus the transverse magnetization induced by preceding excitations in order to encode $T_2$. Although it is still possible to interweave multiple RF coil configurations, this would entangle the relative transmit phase between excitations into the fingerprint, which would expand the size of the database required for fingerprint matching. Instead, we simply dedicate a single RF coil configuration to each of these two segments (Supplementary Fig. 7). This way, even if an RF void exists in one of the illuminations, the fingerprints remain viable, provided that the other illumination does not have an RF void in precisely the same place.

To quantify $T_1$ and $T_2$ accurately, the fingerprint must sample the spin dynamics over a time interval comparable to (or exceeding) the longest expected relaxation time. Instead of acquiring one long continuous fingerprint, a delay time ($t_M$) is inserted between the segments during which the magnetization is allowed to partially recover (Supplementary Fig. 7). This has three advantages. First, it strongly encodes $T_1$ without depositing additional RF energy into the sample. Second, it allows the longitudinal magnetization to regrow, which translates to larger signal amplitudes in later sections of the fingerprint. Third, this time can be used to measure additional segments corresponding to two more slices. At 3 T, most human tissues cannot relax completely during this delay. Consequently, the second segment of every segment is dependent on the previous segment, that is, all four segments collectively form one MR fingerprint that simultaneously identifies the underlying $B_1^+$ distributions and tissue properties ($PD$, $T_1$ and $T_2$).

The second and fourth segments contain larger driving voltages to emphasize the refocusing component. The exact relative driving voltages and phase increments can be found in the Supplementary Data 1. Before each examination, the relative drive voltages are scaled by the inline RF transmit adjustment available on all MR systems. Owing to the relatively large dynamic range of driving voltages in the sequence, this need not be precise. When using a 2 ms sinc pulse with a time-bandwidth product of 3, a peak $B_1^+$ product between 3 and 4.5 MHz in either illumination is sufficient to produce accurate multiparametric maps (Fig. 6c–f).

**Spatial encoding and intermediate image reconstruction.** Fully sampling all 480 time points with a clinically acceptable matrix size $M \times M$ would result in an impractically long scan time. Instead, we only acquire a small number ($N$) of radial samples (spokes). Traditionally, the use of such an extreme acceleration factor ($R$), as defined in equation 1, would result in insurmountable streak-like aliasing artefacts. In the MRF framework, however, these incoherent artefacts add a noise-like modulation to the fingerprint, which has a relatively benign effect on the reconstruction process.

$$R = \frac{M \times \pi}{2 \Delta N}$$

Each time point in the fingerprint is sampled with $N$ evenly distributed radial spokes (Supplementary Fig. 8a). To emphasize the incoherence between aliasing artefacts, the readout is rotated by $14 \times 6/7$ degrees between excitations. This ensures that subsequent time points cover complementary regions of k-space (Supplementary Fig. 8b). In turn, this enforces a different distribution of streak-like artefacts between exposures in the image domain (Supplementary Fig. 8c). The images from which the fingerprints are extracted are reconstructed using a non-uniform fast Fourier transform (FFT) augmented with parallel imaging (see Fig. 7). The parallel imaging strategy is optional, since the matching process itself can filter out most aliasing (see also Supplementary Note 5 and Supplementary Table 3).

The image reconstruction process was implemented in Matlab (The MathWorks Inc., Natick, MA, USA).

**Dictionary construction.** The database with simulated MR fingerprints, hereafter referred to as the dictionary, was computed based on our extended-phase graph formalism. For the in vivo and in vitro experiments (as opposed to the in silico experiments), the slice profile was incorporated into the simulation based on the Fourier transform of the RF waveform. The final fingerprint is the sum of the different contributions under the slice profile after each excitation. The extended-phase graph simulation software was developed in-house and was written in C++.

The final dictionary has four dimensions: $T_1$, $T_2$ and $B_1^+$ amplitude for each of the two transmit channels. (The PD is derived from the ratio between the measured and simulated fingerprints.) Because of the high dimensionality of this space, the number of values along each axis needed to be constrained. To maintain constant relative accuracy, we incremented the $T_1$ and $T_2$ values in steps of 5%. $B_1^+$ values ranged from 150 to 4,564 ms, and $T_2$ values ranged from 15 to 456 ms. $B_1^+$ values were evenly distributed between 0 and 15 $\mu$T in increments of 0.2 $\mu$T. The database was compressed, as described in the next section, and was permanently stored. In total, the dictionary contained over 107 entries, and was ≤5 GB in size (after compression). Using a four-core laptop computer running at 2.4 GHz, the approximate calculation time for the dictionary was ≈2 h without the slice profile, and ≥10 h when the slice profile was included. Note that this pre-computation step is performed only once. It has no impact on the reconstruction time or scan duration, and it can be used to reconstruct all future measurements.

**Fingerprint compression.** Both simulated and measured fingerprints were compressed before dictionary matching. This compression step serves two purposes. First, it accelerates the matching process by reducing the number of data points in each fingerprint. Second, it alleviates computer memory constraints by reducing the size of the dictionary. Both of these two properties are particularly

| Method | Matrix size | Scan time per slice (s) |
|--------|-------------|-------------------------|
| MRF (Ma et al.) | 128 × 128 | 12 |
| MRF (Jiang et al.) | 256 × 256 | 13 |
| PnP-MRF (R = 28) | 160 × 160 | 21 |
| PnP-MRF (R = 50) | 160 × 160 | 12 |
| PnP-MRF (R = 84) | 160 × 160 | 7 |
used in the context of PnP-MRF, where each additional independent RF source adds one more dimension to the dictionary. McGivney et al. demonstrated a mathematically rigorous MR fingerprint compression framework using the singular value decomposition (SVD). However, unlike conventional MR fingerprints, a PnP-MR fingerprint contains signals generated with different transmit channels. The SVD compression can mix these signals, which would entangle the relative transmit phases into the compressed fingerprint. Instead, we implemented a heuristic fingerprint compression method based on the concept of k-space view-sharing. The procedure simply integrates sets of 15 consecutive complex sample points obtained with the same RF coil configuration. After compression, each fingerprint is reduced from 480 to 32 time points (Supplementary Fig. 9). The number of projections and integration intervals were chosen based on prior experimentation, and should not be viewed as the result of a mathematically rigorous optimization process. Future work could improve on this by extending the SVD-based compression to the PnP-MR framework. This view-sharing-based compression can further reduce the size of the dictionary by projecting the matching processes from a complex space (phase and amplitude) on a real space. After compression, the incoherent contributions due to aliasing artefacts interfere (Supplementary Fig. 8c vs d). Under ideal conditions, and using a matched-filter coil combination to remove the relative transmit and receive phase contributions, this results in a real-valued compressed fingerprint. In practice, some phase variations and residual aliasing artefacts remain (Supplementary Fig. 8d). Empirically we found that remaining phase variations can safely be disregarded by taking the absolute value. After compression, the size of the database is reduced by a factor of 30 (the projection from complex to real values reduces the dictionary size by a factor of 2, and bundling 15 time points together reduces the dictionary size by another factor of 15). Moreover, the same compression process respectively applied to the dictionary is also applied to measured fingerprints. As noted in ref. 45, the compression can be performed in k-space directly, thus reducing the number of non-uniform Fourier transforms needed to reconstruct the final maps.

Matching algorithm. The synthetic maps (TI, T2 and B1+) were extracted by identifying the (compressed) dictionary element that best correlates with the (compressed) measured fingerprint. Once the best matches are found, the PD map is retrieved by calculating the ratio between the measured (un-normalized) and simulated (un-normalized) fingerprints. The system-dependent variations due to the spatial distribution of receive sensitivity profile were removed using coil sensitivity estimates derived from the central k-space portion in the first compressed projection from complex to real values reduces the dictionary size by a factor of 2, this results in a real-valued compressed fingerprint. Instead, we implemented a heuristic fingerprint compression method using the singular value decomposition (SVD). However, experiments were not performed in an interleaved manner, that is, one slice was acquired before the next, one slice every 2 min. The slices were positioned to coincide with the slices in the PnP-MRF data set. In addition, we also obtained a PD-weighted TSE image from a separate scan session with exactly the same set-up. Sequence parameters were as follows: turbo factor 5, TR/TE = 4.000/8.4 ms, 320 × 320 matrix, 1.5 × 1.5 mm2 in-plane resolution and 5 mm slice. During all the experiments, the online-specific absorption rate estimation remained well below 50% of the (normal) limit. The study was approved by our institutional review board, and written informed consent was obtained before each examination.

Phantom experiments at 3 T. Phantom experiments were performed using the same MR system described above, paired with a 20-channel head receive coil. All measurements were performed in a single session, after the phantom had acclimatized to the ambient temperature. The phantom contained seven test tubes (2.5 cm diameter), each filled with distilled water doped with different concentrations of manganese (II) chloride tetrahydrate (\(\text{MnCl}_2\)·\(4\text{H}_2\text{O}\), Sigma-Aldrich, St. Louis, MO) and in the phantom, the basis field was 3 Tesla. For the phantom experiments, the center 16.5 × 20.0 cm cylindrical container, was filled with a mixture of distilled water, Gadoxilum (Magnevist, Bayer Healthcare, Germany) and manganese (II) chloride tetrahydrate to create a distinct background. Sequence parameters for our PnP-MRF sequence were as follows: TR/TE = 4.8/2.3 ms, 18 slices, a 160 × 160 matrix, 1.5 × 1.5 mm2 in-plane and a 5.0 mm slice thickness. The experiment was repeated three times: once with an acceleration factor of 28 (nine spokes per illumination, ± 21 s per slice), once with an acceleration factor of 50 (five spokes per illumination, ± 12 s per slice) and once with an acceleration factor of 84 (three spokes per illumination, ± 7 s per slice). To avoid air bubbles and partial volume effects from the porous 3D printed spacer, only the centre slice was used in the validation. Each tube was manually segmented to create seven ROIs (a ± 2.5 mm diameter disk matching the cross-section of each tube, 160 voxels).

The simulated B1+ profiles were used to perform synthetic MR experiments in an axial slice through the abdomen based on the extended-phase graph formalism. Each of the tissues in the body model was assigned literature T1, T2 and PD values corresponding to 1.5 T (refs 52,53). Although T1 and T2 values are field strength-dependent, we kept the values constant to better visualize the impact of B1+.
bias because of environmental factors such as scanner/phantom temperature drift. Each measurement was reconstructed with and without parallel imaging. For every measurement, the T1 and T2 values in each ROI (≥ 100 voxels ROI) were averaged to evaluate the reproducibility/precision. In addition, the histogram of all voxels in each ROI was computed.

Phantom experiments at 7T. A 60 cm diameter bore 7 T MRI system (Magnetom 7T, Siemens) was used to compare the performance of MRF and PnP-MRF in the presence of heterogeneous B0 fields. An in-house developed build-8-channel dipole array head-coil was used to image the same phantom as described above. Note, however, that the T1 and T2 values are expected to be different because of the increased magnetic field strength, and significantly reduced room temperature.

The conventional MRF sequence design and reconstruction method was implemented as described in ref. 34, except for the k-space sampling pattern. To avoid artefacts due to eddy currents and B0 variations, which are more prominent at 7T, we replaced the variable density spiral sampling of k-space with a golden angle radial sampling. Five radial spokes were collected per time frame (total of 5 × 1,000 radial samples), which results in an effective undersampling factor of 20. These five spokes were acquired sequentially, allowing the spins to relax back to equilibrium (10 s) before repeating the RF pulse train. The sequence parameters were as follows: matrix size 160 × 160, 1.5 × 1.5 mm2 voxel size, 5-mm-thick slice and one slice. The total scan time was ≤2 min.

Approximately the same total number of spokes was used in the PnP-MRF measurement (none spoke per time frame for a total of 9 × 480 radial samples). The sequence parameters were as follows: TR/TE = 6/2.1 ms, matrix size 160 × 160, 1.5 × 1.5 mm2 voxel size, 5-mm-thick slice and six slices. The total scan time was ≤3 min (30 s per slice). The approximate CP and gradient coil modes used in the PnP-MRF sequence were obtained using a quick calibration scan (total scan time 7 s). This scan consists of a basic gradient echo sequence, which automatically obtains one low-resolution image for each of the eight available transmit channels. The sequence parameters for this calibration scan were as follows: TR/TE = 6/2.5 ms, matrix size 128 × 128, 2.3 × 2.3 mm2 voxel size, 20-mm-thick slice, one slice. A simple Bash script installed on the host computer of the MR system extracts the different RF phases measured for the centre of image and calculates the offset necessary to approximate the CP mode. These values are written to a file and automatically incorporated into every subsequent PnP-MRF scan.

Data availability. All data that support the findings of this study are available from the corresponding author upon request.

Code availability. All data and codes necessary for sequence implementation, sequence simulation, dictionary creation and image reconstruction are freely available on Bitbucket (https://bitbucket.org/macloos/pnp-mrf/wiki/Home/).

References

1. Yarnykh, V. L. Actual flip-angle imaging in the pulsed steady state: a method for rapid three-dimensional mapping of the transmitted radiofrequency field. Magn. Reson. Med. 57, 192–200 (2007).
2. Schär, M., Vonken, E. & Stuber, M. Simultaneous B0 field mapping for simultaneous B0 correction and image reconstruction. Magn. Reson. Med. 56, 620–629 (2006).
3. Massire, A. et al. Parallel-transmission-enabled three-dimensional T2-weighted imaging of the human brain at 7 Tesla. Magn. Reson. Med. 73, 2195–2203 (2014).
4. Cloos, M. et al. Parallel-transmission-enabled magnetization-prepared rapid gradient-echo T1-weighted imaging of the human brain at 7T. NeuroImage 62, 2140–2150 (2012).
5. Ma, D. et al. Magnetic resonance fingerprinting. Nature 495, 187–192 (2013).
6. Chen, Y. et al. MR fingerprinting for rapid quantitative abdominal imaging. Radiology 279, 278–286 (2016).
7. Buononcini, G. & Sawiak, S. J. MR fingerprinting with simultaneous B1 estimation. Magn. Reson. Med. doi:10.1002/mrm.26009 (2015).
8. Hoult, D. I. The solution of the Bloch equations in the presence of a varying B1 field – an approach to selective pulse analysis. J. Magn. Res. 35, 69–86 (1979).
9. Alagappan, V. et al. Degenerate mode hand-pass birdcage coil for accelerated parallel excitation. Magn. Reson. Med. 57, 1148–1158 (2007).
10. Bottomley, P. A. Turning up the heat on MRI. J. Am. Coll. Radiol. 5, 853–855 (2007).
11. Hofmann, J. et al. Safety testing and operational procedures for self-developed radiofrequency coils. NMR Biomed. doi:10.1002/nbm.3290 (2015).
12. Voigt, T., Katscher, U. & Doessel, O. Quantitative conductivity and permittivity imaging of the human brain using electric properties tomography. Magn. Reson. Med. 66, 456–466 (2011).
13. van Lier, A.L.H.W. et al. Electrical properties tomography in the human brain at 1.5, 3, and 7T: a comparison study. Magn. Reson. Med. 71, 354–363 (2013).
14. Lu, Y., Li, B., Xu, J. & Yu, J. Dielectric properties of human glioma and surrounding tissue. Int. J. Hyperther. 8, 755–760 (1992).
15. Haemmerich, D. et al. In vivo electrical conductivity of hepatic tumours. Physiol. Meas. 24, 251–260 (2003).
16. Victoria, T. et al. Fetal magnetic resonance imaging: jumping from 1.5 to 3 tesla imaging: a preliminary experience. Pediatr. Radiol. 44, 376–386 (2014).
17. Jiang, Y., Ma, D., Seiberlich, N., Gulani, V. & Griswold, M. A. MR fingerprinting using fast imaging with steady state precession (FISP) with spiral readout. Magn. Reson. Med. 74, 1621–1631 (2015).
18. Dixon, W. C. Simple proton spectroscopic imaging. Radiology 153, 189–194 (1984).
19. Reeder, S. B. et al. Water/fat separation with IDEAL gradient-echo imaging. J. Magn. Reson. Imag. 25, 644–652 (2007).
20. Lauterbur, P. C. Image formation by induced local interactions: examples employing nuclear magnetic resonance. Nature 242, 190–191 (1973).
21. Mansfeld, P. & Graenell, P. K. NMR 'diffraction' in solids. J. Phys. C Solid State Phys. 6, L422–L426 (1973).
22. Fessler, J. A. & Sutton, B. P. Nonuniform fast fourier transforms using min-max interpolation. IEEE Trans. Signal Process. 51, 560–574 (2003).
23. Sidickson, D. K. & Manning, W. J. Simultaneous acquisition of spatial harmonics (SMASH): fast imaging with radiofrequency coil arrays. Magn. Reson. Med. 38, 591–603 (1997).
24. Pruessmann, K. P. & Weiger, M. SENSE: sensitivity encoding for fast MRI. Magn. Reson. Med. 42, 952–962 (1999).
25. Griswold, M. A. et al. Generalized autocalibrating partially parallel acquisitions (GRAPPA). Magn. Reson. Med. 47, 1202–1210 (2002).
26. Pruessmann, K. P., Weiger, M., Börnert, P. & Boesiger, P. Advances in sensitivity encoding with arbitrary k-space trajectories. Magn. Reson. Med. 46, 638–651 (2001).
27. Weigl, M. Extended phase graphic dephasing, RF pulses, and echoes - pure and simple. J. Magn. Reson. Imaging 41, 266–295 (2014).
28. McGivney, D. F. et al. SVD compression for magnetic resonance fingerprinting in the time domain. IEEE Trans. Med. Imaging 33, 2311–2322 (2014).
29. Song, H. K. & Dougherty, K. L. k-space weighted image contrast (KWC) for contrast manipulation in projection reconstruction MRI. Magn. Reson. Med. 44, 825–832 (2000).
30. Boesiger, P. B., Edelstein, W. A., Hayes, C. E., Souza, S. P. & Mueller, S. P. The NMR phased array. Magn. Reson. Med. 16, 192–225 (1990).
48. Walsh, D. O., Gmitro, A. F. & Marcellin, M. W. Adaptive reconstruction of phased array MR imagery. Magn. Reson. Med. 43, 682–690 (2000).
49. Cauley, S. F. et al. Fast group matching for MR fingerprinting reconstruction. Magn. Reson. Med. 74, 523–528 (2015).
50. Christ, A. et al. The virtual family - development of surface-based anatomical models of two adults and two children for dosimetric simulations. Phys. Med. Biol. 55, N23–N38 (2010).
51. Setsompop, K. et al. Slice-selective RF pulses for in vivo B1\(^+\) inhomogeneity mitigation at 7 tesla using parallel RF excitation with a 16-element coil. Magn. Reson. Med. 60, 1422–1432 (2008).
52. Stanisz, G. J. et al. T1, T2 relaxation and magnetization transfer in tissue at 3T. Magn. Reson. Med. 54, 507–512 (2005).
53. Bazelaire, C. M. J., Duhamel, G. D., Rofsky, N. M. & Alsop, D. C. MR imaging relaxation times of abdominal and pelvic tissues measured in vivo at 3.0 T: preliminary results. Radiology 236, 652–659 (2005).
54. Shellock, F. G. Biomedical implants and devices: assessment of magnetic field interactions with a 3.0-Tesla MR system. J. Magn. Reson. Imaging 16, 721–732 (2002).
55. Barral, J. et al. A robust methodology for in vivo T1 mapping. Magn. Reson. Med. 64, 1057–1067 (2010).

**Acknowledgements**

This work was supported in part by NIH R21 EB020096, NIH R01 EB011551 and Siemens Healthcare and was performed under the rubric of the Center for Advanced Imaging Innovation and Research (CAI^3^R, https://www.ca3r.net), a NIBIB Biomedical Technology Resource Center (NIH P41 EB017183). We also thank José Raya for discussions regarding this work; Bei Zang for providing the RF coil simulations; and Pawel Slabisk and Dmitry Novikov for their assistance in preparing the manuscript.

**Author contributions**

M.A.C. with the aid of G.C.W., T.Z. and M.B. performed the experiments. M.B. identified implants suitable for the experiment, consented the volunteers and supervised safety. M.A.C. and T.Z. consulted K.T.B. and implemented the magnetic resonance sequence. M.A.C., K.T.B. and F.K. implemented the image reconstruction process. M.A.C., F.K., T.J., M.B., G.C.W. and D.K.S. analysed and interpreted the data. M.A.C. worked with M.B. G.C.W. and D.K.S. to design the experiments. M.A.C. and D.K.S. wrote the paper.

**Additional information**

**Supplementary Information**

Supplementary Information accompanies this paper at http://www.nature.com/naturecommunications

**Competing financial interests:** The authors declare no competing financial interests.

**How to cite this article:** Cloos, M. A. et al. Multiparametric imaging with heterogeneous radiofrequency fields. Nat. Commun. 7:12445 doi: 10.1038/ncomms12445 (2016).

This work is licensed under a Creative Commons Attribution 4.0 International License. The images or other third party material in this article are included in the article's Creative Commons license, unless indicated otherwise in the credit line; if the material is not included under the Creative Commons license, users will need to obtain permission from the license holder to reproduce the material. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/