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T_1-T_2 Dual-Modal Magnetic Resonance Imaging: From Molecular Basis to Contrast Agents

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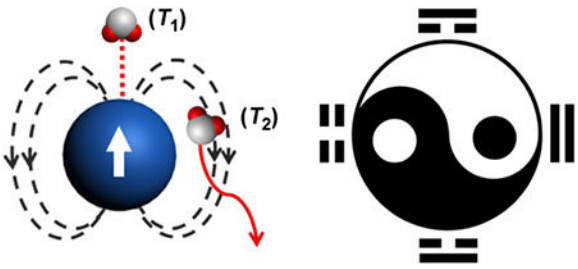
Abstract

Multi-modal imaging strategies integrating multiple imaging modalities have been recognized with improved feasibility in diagnosis, guiding therapy, and predicting outcomes. Magnetic resonance imaging (MRI) permits multi-parameter demonstration of anatomical structures, such as the T_1 bright and T_2 dark MRI programs. Due to the inherent black-and-white production of MR images, however, MRI detection is partially limited by the occurrence of false-positive diagnosis. Here, we introduce an interesting dual-modal program based on T_1-T_2 dual-modal MRI and the enhancement by contrast agents. We will focus on the interplay of T_1 and T_2 relaxation mechanism, which features the origin of T_1-T_2 dual-modal MRI from molecular basis to contrast agents. The discussion made in this Perspective paper may help to understand the T_1-T_2 dual-modal MRI and provoke the rational design of the contrast agents for sophisticated MRI applications.

Graphical Abstract



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Since the first introduction of X-ray imaging, medicine has long been relying on molecular imaging techniques throughout the decision-making processes of diagnosis and prognosis.[1–3] Along with the development of singular medical imaging methods, one of the most fascinating research fields is the development of multimodal imaging strategy to upgrade diagnostic accuracy.[4] The increasing needs for imaging subtle details in clinical diagnosis further stimulate the essential requirement of multimodal imaging techniques in cutting-edge.[5–7] The Imaging Council of the American College of Cardiology was in agreement that "multimodality imaging is the efficient integration of various methods of cardiovascular imaging to improve the ability to diagnose, guide therapy, or predict outcomes".[4] In general, multimodal imaging program benefits from the cross-validation of multiple parameters which are considered capable of making their individual advantages complementary to each other. The mutual confirmative diagnostic information by multiple imaging modalities holds great potential to exclude false-positive diagnosis as of singular imaging method. For example, the combination of positron emission tomography (PET) and computerized tomography (CT) or magnetic resonance imaging (MRI) for precise pinpointing region of interest with both molecular sensitivity and anatomic resolution.[8]

Advances in nanomedicine have spurred a number of nanomaterials as imaging agents to further augment the diagnostic sensitivity and accuracy.[9, 10] However, contrast agents designed for multimodal imaging purposes have faced a lot of complicated situations.[11, 12] For example, probes for PET can be 5~8 orders of magnitude more sensitive than those for MRI, which may lead PET-MRI dual-modal contrast agents to inadequate MRI detection at a low concentration and/or burdened radioactive PET tracers in an unnecessarily high level. Therefore, tying multiple imaging techniques together should avoid combining functions simply for convenience.[12] Moreover, the past decades have witnessed multifarious design considerations of combining different imaging techniques in pre-clinical research, from dual-modal to hexa-modal combinations.[13–16] Among the variety of multimodal imaging strategies, however, very few of them have earned admittance to clinical applications because of the mostly unparalleled spatial-temporal resolution and sensitivity from difficult imaging techniques. Image registration and comparsion across various imaging modalities are still challenging and time consuming now. In this Perspective paper, we introduce an interesting dual-modal imaging paradigm, T_1-T_2 dual-modal MRI, achieved by a MRI machine alone.

T_1-T_2 DUAL-MODAL MRI

MRI is a noninvasive, non-ionized, and radiation-free technique that enables to reconstruct atomic nuclear magnetization signal into 2D/3D images, which is the most widely used anatomic tools in clinical diagnosis.[17] The regular imaging protocols in MRI can be subdivided into weighted imaging based on longitudinal (T_1) or transverse (T_2) relaxation times, molecular diffusion, proton density, etc. The advantage of MRI is its high sensisitivity to soft tissue and its flexibility in designing contrast mechnishm of MRI images for various purpose. For example, T_1 characterizes the time needed in the recovery of the longnitudinal magnetization from its excitation state to its equilibrium state after excitation with RF pulse, which is quite different among tissue types naturally and is commonly used in brain anatomic images. On the other hand, T_2 characterizes the time needed for

the transverse magnetization decaying to zero, which is also strongly dependent on tissue types. T_1-weighted MRI is normally achieved by inversition-recovery MRI pulse sequences ref for MPRAGE sequence , which shows darker for longer T_1, whereas T_2-weighted MRI is normally achieved by echo time (TE) weighted MRI pulse sequences, which shows brigher for longer T_2 ref for FLA1R sequence.

Another commonly used imaging procedure is proton density weighted MRI, which was designed to minimize the T_1 and T_2 effects using optimal parameters, generating an image dependent primarily on the density of protons of the imaging volume. Besides, there are lots of other imaging sequences developed as parameter packages for different imaging purposes.

Recently, novel MRI sequences that enables quantitatively parametrical imaging with clinically feasible time are also avalible, i.e., the paramters, like T_1 and T_2, can be quantitatively mapped rather than using the parameter-weighted imges. What's more, the T_1 and T_2 can be quantitatively mapped simutanously in a single MRI sequence.(1, 2)

Lesion detection in practice requires multiscale integration of diagnostic information. The goal of all imaging strategies is to display contrast in images, which should emphasize certain contrast characteristics of anatomical structures and allow doctors to differentiate which structures are abnormal.[18] Under an MR imaging session, both T_1 and T_2 weighted images can be obtained using one MRI machine by simply adjusting the acquisition sequences, even simultaneously with same spatial sampling (1). The combined T_1 and T_2 dual-modal MRI is considered with self-confirmed merits in practical diagnosis. Distinctly different from other dual-modal imaging strategies involving two different machines, T_1-T_2 dual-modal MRI performed on one machine promises to offer an accurate match of spatial and temporal imaging parameters between each other.[19, 20]

The imaging protocol made by MRI practitioners is highly dependent on their own empirical judgment. In general, T_2 imaging protocol is used to assess water content which appears bright signal, while T_1-weighted imaging is useful for assessing tissues with high fat contents, such as brain white matters. In many cases, both T_1 and T_2 MR images will be obtained in order to cross-validate the possible fault-positive information. Taking brain MRI diagnosis for an example, T_1 image is acquired to differentiate gray matters between potential lesions and T_2 image is used to show the cerebrospinal fluid (CSF) in the brain tissue. Owing to the precise tomographic algorithm of MRI, both T_1 and T_2 images of every slices can find exact match between each other, which accumulate the advantages of self-confirmed fault-free diagnosis. Although the procedure of T_1-T_2 dual-modal MRI has not gained acceptance as a standard, the combination of multiple contrast MR images in a way have potentiated the advantages of MRI diagnosis to its maximum extend.

MOLECULAR BASIS

MRI is usually default as referring to ^{1}H MRI because ^{1}H is the most widely studied (largest gyromagnetic ratio) and abundantly existed nucleus in human body. Other magnetic nucleus (e.g., ^{19}F) obey the same rules as for ^{1}H protons. In a typical MRI program, nucleus process around an axis along the direction of an external magnetic field, which features

a Boltzmann equilibrium state with nucleus separated by the Zeeman splitting effect into high and low energy states. The net magnetization of this state is parallel to the external magnetic field. Subsequently, a radiofrequency pulse of 90 degrees perpendicularly to the external magnetic field is applied, which flips over the magnetization from longitudinal (z) direction to transverse (xy) plane. Afterwards, the tendency of nucleus to return to its equilibrium state makes up the definition of nuclear magnetic relaxation, including the magnetizations at xy plane and z direction (Figure 1a,b). To simplify, R_1 and R_2 were artificially nominated to represent for relaxation rate constants at z direction and xy plane, respectively. Correspondingly, the time it takes for longnitudinal magnetization recover to 63% or *transverse magnetization* decay to 37% of its original state were denoted as T_1 and T_2 relaxation time, respectively. Typically, T_1 and T_2 relaxation time differs from each other and varies in different subjects, which is dependent on the spin-lattice and spin-spin interactions between components and surroundings, respectively. A majority of T_1 or T_2 relaxation times recorded in routine MRI programs are between several microseconds to seconds.

From a molecular viewpoint, spin-lattice (T_1) relaxation implies energy exchange of spins with environment, while spin-spin (T_2) relaxation is the loss of phase coherence as spins interacting with each other and surrounding environments. Therefore, it is conceivable that factors causing T_1 relaxation will also influence T_2 relaxation, whereas some factors that cause T_2 relaxation do not involve T_1 relaxation, such as static dipolar fields created by neighboring dipoles. Therefore, in most cases but not in principle, the T_2 for a given object is always shorter than its T_1 relaxation time. It is noteworthy that T_1 and T_2 relaxations take place independently and immediately after the removal of the 90 degrees radiofrequency pulse. However, only magnetization at transverse plane (T_2) can be directly recorded by MRI machine because it exactly perturbs the external magnetic field when it is decaying. To measure magnetization at longitudinal direction (T_1) which is parallel to the external magnetic field, another radiofrequency pulse is needed to flip over the restored magnetization at longitudinal direction to transverse plane (Figure 1b). Assuming that an object has larger R2 (shorter T_2), its longitudinal magnetization can be partially attenuated by the strong T_2 decaying effect when it is measured at the transverse plane after magnetization flipping. Therefore, MRI physicists and radiologists usually have to tune the parameters on each MRI sequence or design new MRI sequence to acquire MRI with satisfied imaging contrast.

A general procedure of T_1-T_2 dual-modal MRI strategy is to acquire T_1 and T_2 MRI successively in one MRI study. However, reliable contrasts for T_1 bright and T_2 dark images are highly dependent on the interplay between the intrinsic T_1 and T_2 relaxation times of region-of-interest, which are determined by the structural features of the region-of-interest as well as the magnet strength of MRI scanner. In an extreme circumstance, T_1-T_2 dual-modal MRI should avoid to obtain dual-dark or dual-bright T_1-T_2 images, which otherwise would cause ambiguous illustration and therefore the loss of mutual confirmative merits in practice. This phenomenon could happen when a tissue has extremely long T_1 and short T_2 relaxation times (resulting in dual-dark T_1-T_2 images), or has extremely short T_1 and long T_2 relaxation times (resulting in dual-bright T_1-T_2 images). As we noted above, short T_2 relaxation time would largely attenuate T_1 signal under MRI test. An ideal T_1-T_2 dual-modal

MRI program is thus desirable for tissues with moderate T_1 and T_2 relaxation times, for examples, liver, kidney, muscle, and brain matters with T_1 of 500-900 and T_2 of 40-80 ms at a magnet field of 1.5 T. Pathological abnormalities or inflammations usually accompany with water content alternation. Because free water has both long T_1 and T_2 relaxation times, which are both of about 3 s, which may appear dark in T_1 and bright in T_2 images. By T_1-T_2 dual-modal MRI, it is assumable that the diagnostic accuracy can be largely augmented by orthogonal complement of T_1 and T_2 signal contrasts between normal and abnormal tissues.ref?

CONTRAST AGENTS

Contrast agents are a series of materials enabling to generate imaging contrasts between the region-of-interest and the surroundings. The mechanism of MRI contrast agents is to alter the magnetization relaxation at T_1 and T_2 planes, wherein the effectiveness is determined by its relaxivity r_1 and r_2 values, respectively.[21, 22] Magnetic materials are usually assorted as T_1 or T_2 contrast agents based on their dominated function in T_1 or T_2 MRI. Empirically speaking, T_1 contrast agents are usually paramagnetic metal-chelating molecules (e.g., Gd^{3+}, Mn^{2+} chelates) or organic radicals, which shorten T_1 and cause bright contrast in conventional T_1-weighted image;[23, 24] T_2 contrast agents are usually superparamagnetic nanoparticles (e.g., Fe_3O_4, FeC_x), which give dark contrast in T_2-weighted image.[22, 25] We briefly summarized here that T_1 contrast enhancement is mainly related to the direct chemical exchange of protons with the paramagnetic centers at the innersphere regime, and T_2 is mainly attributed to the proton's effective diffusion and interaction with the magnetic dipolar moment at the outersphere regime (Figure 1c).[26] Although both T_1 and T_2 contrast agents have individual r_1 and r_2 values, few of them is able to exhibit feasible dual-modal contrasts. The reason is complicated in physics and can be easily understood by the followings: (i) T_1 contrast agents usually have low r_2 values, less than 10 $mM^{-1}s^{-1}$ for most of Gd chelates, which make it have very limited effect (i.e., percentage change) on R_2 , while the effect on R_1 is large enough to visibal contrast on T_1-weighted images, due to the fact that the natural R_1 (without contrast agent) is much smaller than R_2; (ii) T_2 contrast agents have apparently high r_2 value, hundreds to thousands $mM^{-1}s^{-1}$, which significantly constrained the T_1 contrast even though their r_1 values are not necessarily low.

The past decades have witnessed a number of design and applications of T_1-T_2 dual-modal MRI contrast agents, which are eligible to show both T_1 bright and T_2 dark contrasts.[19, 20, 26–31] Due to the relatively different performance of T_1 and T_2 contrast agents, one can simply realize that integrating both T_1 and T_2 contrast materials into one nanoentity could achieve both T_1 and T_2 contrast abilities. For example, Cheon group reported that $MnFe_2O_4$@SiO_2 nanoparticles decorated with Gd agents showed distance-dependent T_1-T_2 dual-modal contrast logics by modulating the thickness of the SiO_2 layer.[20] Most recently, the same group reported the utilization of distance-dependent magnetic resonance tuning for sensing a wide range of biological targets.[32] However, this strategy is established on the compromising of T_2 contrast ability to minimize the quenching effect to T_1 contrast.[20, 29] Alternatively, Gao group reported a serious of Gd_2O_3 nanocrystals embedded iron oxide nanostructures which exhibited mutual-enhanced T_1 and T_2 contrast ability compared with that of their single components.[19, 28, 33, 34] Besides the paradigm of combining T_1 and T_2

contrast agents, it was found that certain magnetic nanoparticles inherently display both T_1 and T_2 contrasts, propagating the family and theory of MRI contrast agents.[35] Dated back to a decade ago, Dai group demonstrated that FeCo nanoparticles enabled to serve as both T_1 and T_2 contrast agents, in which the underlying mechanism is still ambiguous.[36] In other attempts, the integration of paramagnetic T_1 contrast materials with nonmagnetic matrix (e.g., polymers, porous silica, proteins) would result geometrically confined diffusion for surrounding water molecules, which in turn manifest T_1-T_2 dual-modal contrast ability of the complex.[37, 38]

Apparently, the mechanism of T_1-T_2 dual-modal MRI contrast agents differs from one to another, whereas a few general rules could be applied for assessing the contrast. First, due to the interference of T_1 relaxation by T_2 decaying effect, magnetic nanoparticles should be optimized with conservative r_2 values to compromise the T_2 decaying effect to T_1 relaxation, which otherwise would vanish the T_1 contrast effect. Second, magnetic nanoparticles with small size or magnetic metal chelates with clustering structure would benefit from the altered structural parameters, which may therefore exhibit T_1-T_2 dual-modal contrasts. Third, the T_1-T_2 dual-modal manner is highly dependent on the magnetic field strength of the used MRI scanner. Due to the fact that stronger magnetic field would have much more significant T_2* effect, which would largely attenuate the T_1 relaxivity especially for nano-sized particles and macromolecules. Last but not least, the optimization of sequences used for acquiring T_1 and T_2 images are required to highlight the differentiation between T_1 and T_2 contrast images. In practice, the optimal concentration of a given T_1-T_2 dual-modal contrast agents should have benefited from the phantom study, which is considered to be critical in this system. The use of dual-modal MRI contrast agents may promise to build up an artificial logic program in MRI program with T_1-T_2 OFF-ON (0-1), ON-OFF (1-0), ON-ON (1-1), OFF-OFF (0-0) states (Figure 1d), featuring the multiple-parameter demonstration of MRI.

CONLUSION AND OUTLOOK

Diagnosis plays a pivotal role in modern medicine, which to some extend will determine the therapeutic process and the outcomes. Different imaging technologies possessing various diagnostic resolution and sensitivity at different levels are often used as a combination to achieve complement accuracy and precision in diagnosis. However, most of the current imaging modalities are difficult to compare the obtained diagnostic information with each other in a parallel level, which underscores the synergistic advantages of combination. On the contrary, T_1-T_2 dual-modal MRI program is able to provide a pair of anatomical images at exactly the same levels but with different contrasts. Further assisted by the contrast agents, this imaging program can output mutual-confirmative information from both the T_1 bright and T_2 dark images of pre-contrast and post-contrast. In this respect, the diagnostic accuracy and precision may be significantly enhanced through the orthogonal algorithms. The development of T_1-T_2 dual-modal contrast agents have attracted numerous attention from chemists and materials scientists for a variety of biomedical applications. After visiting the molecular basis behind T_1-T_2 dual-modal MRI, the evaluation of T_1-T_2 dual-modal contrast efficiency of a given magnetic material should take into considerations the magnetic property, the individual T_2 decaying effect, and the structural parameters. It is of noted that

the study on T_1-T_2 dual-modal MRI program is still in its infant stage due to the lack of clinical verification.

Despite for the low sensitivity of the typical MRI study, the sensitive responsiveness of T_1 and T_2 relaxation to environmental changes have stimulated numerous design of responsive MRI systems for analysis of a wide range of biological targets. However, the large variations during the responsive T_1 or T_2 MRI experiments make it suspicious to the broad applications. The opportunity to use T_1-T_2 dual-modal MRI scheme may shed light to the sophisticated design of responsive MRI systems using orthogonal T_1 and T_2 relaxation changes as two coherence parameters. Therefore, future directions on this topic may focus on the design of T_1-T_2 dual-modal responsive MRI applications. The mutual confirmative logic between T_1 and T_2 relaxation changes would render greatly improved sensitivity and accuracy, which may also open up new avenues to understanding the phenomenon of MRI contrast enhancement by magnetic materials.

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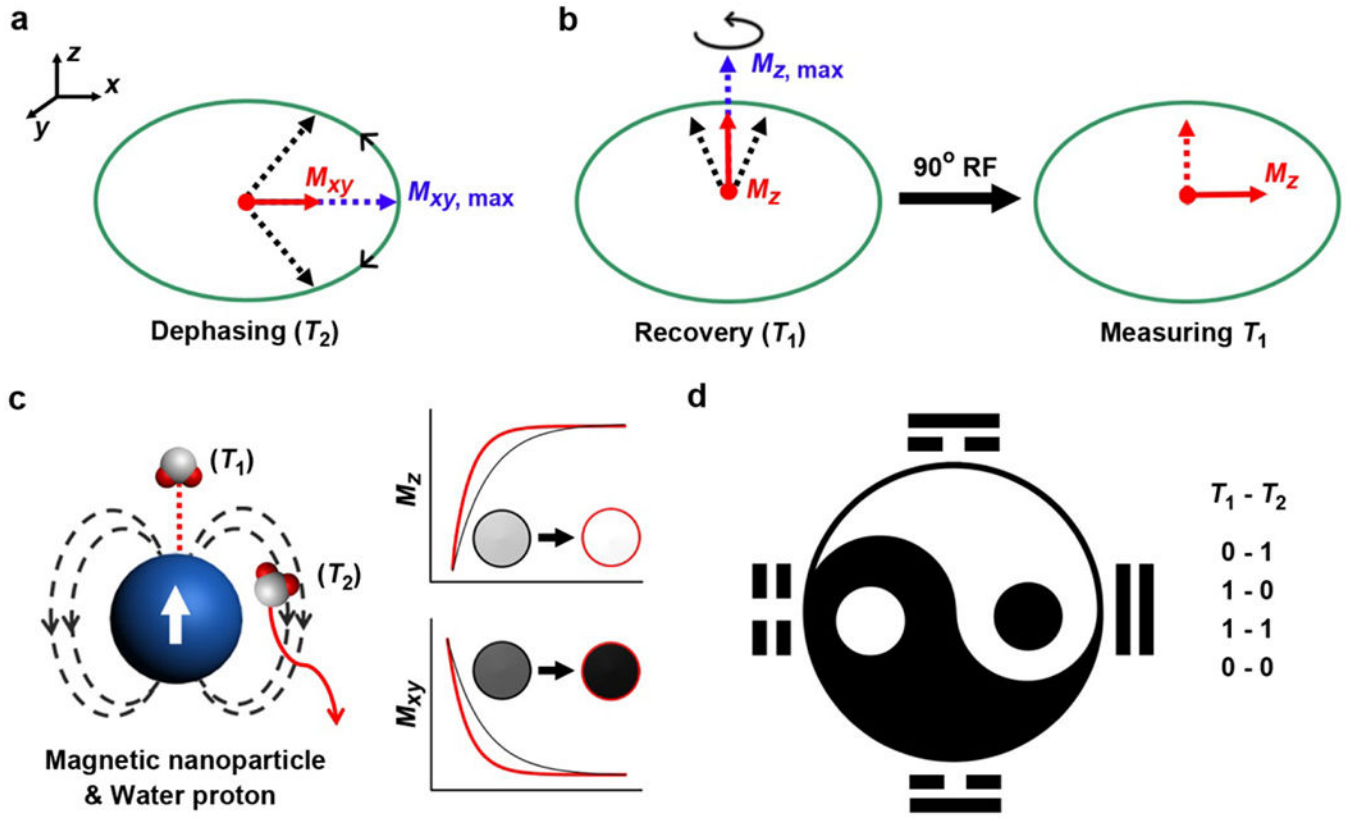

Figure 1:

(a) The phenomenon of T_2 relaxation correlates to the dephasing of the magnetization at *xy* plane (M_{xy}). The $M_{xy,\ max}$ is the M_{xy} immediately after the nuclear magnetic resonance upon a 90° radiofrequency (RF) pulse. (b) The phenomenon of T_1 relaxation describes the recovery of magnetization at *z* direction (M_z) from zero to the $M_{z,\ max}$ along with nuclear spin. A second 90° RF is required to flip over the magnetization from *z* direction to *xy* plane in order to measure the M_z, so that strong T_2 dephasing effect would attenuate T_1 due to this inherent process. (c) The direct coordination with and the diffusion around a magnetic nanoparticle are related to the T_1 and T_2 relaxation enhancement of water protons, respectively. The effective T_1 and T_2 relaxation enhancement result in brighter contrast in T_1 and darker contrast in T_2 imaging. (d) The logic of T_1-T_2 dual-modal imaging can be described as OFF-ON (0-1), ON-OFF (1-0), ON-ON (1-1), OFF-OFF (0-0) states, featuring the multiple-parameter demonstration of MRI.