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Multimodal imaging-based therapeutic fingerprints for optimizing personalized interventions: Application to neurodegeneration

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ABSTRACT

Personalized Medicine (PM) seeks to assist the patients according to their specific treatment needs and potential intervention responses. However, in the neurological context, this approach is limited by crucial methodological challenges, such as the requirement for an understanding of the causal disease mechanisms and the inability to predict the brain's response to therapeutic interventions. Here, we introduce and validate the concept of the personalized Therapeutic Intervention Fingerprint (pTIF), which predicts the effectiveness of potential interventions for controlling a patient's disease evolution. Each subject's pTIF can be inferred from multimodal longitudinal imaging (e.g. amyloid-β, metabolic and tau PET; vascular, functional and structural MRI). We studied an aging population (N = 331) comprising cognitively normal and neurodegenerative patients, longitudinally scanned using six different neuroimaging modalities. We found that the resulting pTIF vastly outperforms cognitive and clinical evaluations on predicting individual variability in gene expression (GE) profiles. Furthermore, after regrouping the patients according to their predicted primary single-target interventions, we observed that these pTIF-based subgroups present distinctively altered molecular pathway signatures, supporting the across-population identification of dissimilar pathological stages, in active correspondence with different therapeutic needs. The results further evidence the imprecision of using broad clinical categories for understanding individual molecular alterations and selecting appropriate therapeutic needs. To our knowledge, this is the first study highlighting the direct link between multifactorial brain dynamics, predicted treatment responses, and molecular alterations at the patient level. Inspired by the principles of PM, the proposed pTIF framework is a promising step towards biomarker-driven assisted therapeutic interventions, with additional important implications for selective enrollment of patients in clinical trials.

Introduction

The top three highest selling drugs for neurological disorders in the US benefit only around 7%–20% of the patients who are treated with them (Schork, 2015). Despite such high failure rates, these drugs are still systematically prescribed by most physicians. Based on the principles of generalized medicine, a plausible justification is the belief that, within a pool of patients sharing a common clinical diagnosis, at least some of them will respond satisfactorily to the standard treatment. In contrast, personalized medicine (PM) is based on the optimization of treatment plans for individual patients through consideration of particular characteristics, including molecular (e.g. genetic), macroscopic (e.g. imaging, physiology) and medical information (Davis et al., 2009; Whitcomb, 2012; Schork, 2015; Carrasco-Ramiro et al., 2017). However, although the principles of PM were proposed decades ago, this approach has not yet become widely established in medical practice. In the neurological context, this delay is linked to critical methodological limitations, notable examples being: i) the common misuse of association analyses

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(e.g. correlation/regression tests) for identifying pathologic causal events and their effects, ii) the incorrect extrapolation of group-based statistical inferences for identifying potential disease biomarkers at the individual level, and, remarkably, iii) the paradoxical confidence in broad clinical/cognitive categories for validating new patient subtypes, often introducing circularity issues in the analyses.

From the molecular to the macroscopic scales, the brain constitutes a complex dynamic system (Bullmore and Sporns, 2009; Sporns, 2011), modulated by intrinsic multifactorial causal interactions and external influences (Iturria-Medina and Evans, 2015; Muldoon et al., 2016; Iturria-Medina et al., 2017a). During the last few decades, we have seen considerable advances in brain modeling using network-based approaches (Rubinov and Sporns, 2010; Iturria-Medina, 2013; Sporns, 2013). Most studies have focused on the spreading of normal and pathologic functional signals (Sotero et al., 2007; Valdes-sosa et al., 2011; Cabral et al., 2012; Sanz Leon et al., 2013; Friston et al., 2014; Iturria--Medina et al., 2014; Sanz-Leon et al., 2015; Stam et al., 2016) and, more recently, on the local interactions among different biological factors (Iturria-Medina et al., 2017a). Dynamic network modeling has contributed significantly to our understanding of dissimilar brain mechanisms, such as the intricate spatiotemporal propagation of neuronal activity (Sotero et al., 2007; Valdes-sosa et al., 2011; Cabral et al., 2012; Sanz Leon et al., 2013; Friston et al., 2014; Sanz-Leon et al., 2015; Stam et al., 2016) or the toxicity of misfolded proteins (Seeley et al., 2009; Iturria--Medina et al., 2014). Moreover, pioneering work has extended previous formulations, relying on the mathematical elegance and validity of the control theory (Kalman, 1963; Klickstein et al., 2016), for predicting the functional and cognitive responses of the brain under the influence of external experimental interventions (Betzel et al., 2016; Muldoon et al., 2016; Tang et al., 2016; Tang and Bassett, 2017). Robust experimental evidence supports the validity of the control principles that characterize and control living dynamic neuronal systems (Tang and Bassett, 2017; Yan et al., 2017). Recently, seeking to incorporate multiple relevant biological factors, rather than only functional neuronal signals (e.g. brain metabolism, vasculature, toxic proteins, and tissue structure), an integrative multifactorial causal model of brain organization and control was proposed (Iturria-Medina et al., 2017a). For each patient, this approach allows accurate characterization of the intra-brain factor-factor causal interactions, the spreading of multifactorial pathologic signals through different brain networks (e.g. axonal and vascular connectomes), and assessment of the effectiveness of either single-target or combinatorial therapeutic interventions (Iturria-Medina et al., 2017a).

Prompted by the urgent demand for identifying effective individualized treatments, here, we introduce and validate the concept of the personalized Therapeutic Intervention Fingerprint (pTIF). Based on the MCM framework and the control theory, the pTIF values are a set of multivariate metrics constructed according to the needed energy required to either stop the patient's pathologic progression or revert its condition to a healthy state. Thus, the pTIF provides a quantitative reflection of the pattern of biological factor-specific deformations required to control the disease evolution in individual patients. It is inferred from individual multimodal longitudinal imaging data (e.g. PET, MRI), characterizing each patient's multifactorial causal interactions and dynamic brain changes in response to potential external (therapeutic) inputs. When applied to an aging and neurodegenerative population (total $N = 331$), the pTIF patterns significantly predict the individual variability in plasma gene expression (GE) profiles and represent a significantly more accurate GE predictor than the traditional clinical/cognitive categories. The pTIF allowed a reliable identification of subgroups of patients with distinctive molecular and macroscopic alterations, allowing to characterize the molecular dysregulations associated to differences in therapeutic needs in a given population. The existence of differential expression in functional molecular pathways among these pTIF-based subgroups indicates the potential of this approach for the detection and characterization of dissimilar disease variants and/or pathologic stages. We further discuss practical implications for the treatment of neurodegeneration. As a multimodal imaging-based approach to PM, the pTIF framework presented here may represent a turning point in the data-driven identification of personalized intervention needs, optimal therapeutic strategies and selective enrollment of patients in clinical trials.

Materials and methods

Ethics statement

The study was conducted according to Good Clinical Practice guidelines, the Declaration of Helsinki, US 21CFR Part 50 – Protection of Human Subjects, and Part 56 – Institutional Review Boards, and pursuant to state and federal HIPAA regulations (adni.loni.usc.edu). Study subjects (Table S1) and/or authorized representatives gave written informed consent at the time of enrollment for sample collection and completed questionnaires approved by each participating site Institutional Review Board (IRB). The authors obtained approval from the ADNI Data Sharing and Publications Committee for data use and publication, see documents http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Data_Use_Agreement.pdf and http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Manuscript_Citations.pdf, respectively.

Data description and processing

Study participants. This study used in total 1006 individual data, with multimodal brain imaging ($N = 944$) and/or blood GE expression data ($N = 744$), from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (adni.loni.usc.edu). The pTIF were estimated and analyzed for 331 participants, with at least four different imaging modalities and four longitudinal data acquisitions, surviving the quality control. A subset of 256 participants with pTIF estimations presented GE from blood samples, and were employed in the differential GE analysis. We also used GE data from 74 additional patients without symptoms of cognitive/clinical deterioration, taken as a reference group for the differential analysis. The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD).

See Fig. S1 for a detailed flowchart of the participant's selection and analysis, and Table S1 for the corresponding demographic characteristics.

Cognitive and clinical evaluations. The participants were characterized cognitively using the mini-mental state examination (MMSE), a composite score of executive function (EF), a composite score of memory integrity (MEM) (Gibbons et al., 2012), and Alzheimer's Disease Assessment Scale-Cognitive Subscales 11 and 13 (ADAS-11 and ADAS-13, respectively). Also, they were clinically diagnosed at baseline as healthy control (HC), early mild cognitive impairment (EMCI), late mild cognitive impairment (LMCI) or probable Alzheimer's disease patient (LOAD).

Blood RNA acquisition/preprocessing. The Affymetrix Human Genome U219 Array (www.affymetrix.com) was used for gene expression profiling from blood samples. Peripheral blood samples were collected using PAXgene tubes for RNA analysis. Total RNA with miRNA retention was extracted using the Qiagen PAXgene Blood RNA MDx Kit (www.qiagen.com) on BioRobot Universal System, with the modifications of manufacturer protocol followed by in-solution Dnase treatment and modified clean up step using Qiagen RNeasy MinElute Cleanup Kit. See (Saykin et al., 2015) for further preprocessing details. The quality-controlled GE data includes activity levels for 49,293 transcripts. Each gene's activity was adjusted for RNA Integrity Number and Plate Number using a robust linear model (Street et al., 1988).