Figure 1 | Development of markers of migraine states. The top two rows show the disease state and potential imaging markers. The row labelled Biomarker criteria summarizes the relative state i.e., phase in the migraine cycle of potential development for each disease state: exploration, demonstration, characterization and surrogacy[165]. The increase in blue density within the triangle represents the overall state of imaging biomarker development. Such markers might be used as a surrogacy for drug evaluation or disease state (improvement) in several contexts, including disease chronification, disease modification or symptomatic treatment.
Key: Δ = change; RSN = resting stat networks; MRS = magnetic resonance spectroscopy; MRI = magnetic resonance imaging

Figure 2 | Definition of MRI measures and examples of brain function and structure in migraine. A | Activation in the thalamus with allodynia. Differences in response of BOLD fMRI signal between the same patients showing responses to allodynia (increased sensitivity to heat stimuli during migraine) are shown in the red-orange regions (adapted from Burstein et al., 2010[44]). B | Parieto-frontal RSN (adapted from Li et al., 2016[183]). The figure shows changes in the specific for the parieto frontal resting state C | Cortical thickening in migraine: the figure shows the region in the post-central gyrus, which is thicker in migraineurs than in controls in high frequency (HF) patients (Adapted from Maleki et al 2012)[57] D | Areas of significant reduced white matter axial (green) and radial (yellow) diffusivity ($P < 0.05$, corrected for family-wise error rate) in pediatric patients with migraine versus healthy controls, superimposed on a fractional anisotropy template in the Montreal Neurological Institute space (Adapted from Messina et al., 2015)[184] E |2D *J*-resolved 1H MRS data recorded from the MRS voxel in a migraine patient (Adapted from Becerra et al., 2016)[185].
Key: BOLD, blood oxygen level dependent; fMRI, functional MRI; CT, cortical thickness; VBM, voxel based morphometry; DTI, diffuison tensor imaging; MRS, magnetic resonance spectroscopy; GABA, gamma amino butyric acid; NAA, n-acetyl aspartate.

Figure 3 | Word cloud of the Gene Ontology, Kyoto Encyclopedia of Genes and Genomes (KEGG) and Reactome pathways enriched in the 37 genes implicated in migraine. The word cloud was generated from the generic enrichment map output from the g:GOSt tool of the g:Profiler web server using the 'wordcloud2' R[186] package (https://github.com/lchiffon/wordcloud2). Colours highlight groups of interest: red indicates vascular-related pathways, blue indicates metal-ion-related pathways, magenta indicates KEGG pathways, green indicates Reactome pathways, and black indicates all other pathways. Character size for a given pathway relates to its enrichment (A larger font indicates greater significance).

Figure 4 | Integrating imaging and genetics into markers of migraine. Numerous processes produce a complex disease that can be dissected using genetic and imaging approaches to define changes that occur in migraine. Predicting changes on the basis of specific markers will improve therapeutic evaluation of treatments for episodic and chronic migraine and the prevention or reversal of disease chronification. Combining genetic markers with an imaging phenotype would lead to greater specificity and reproducibility of a migraine marker.

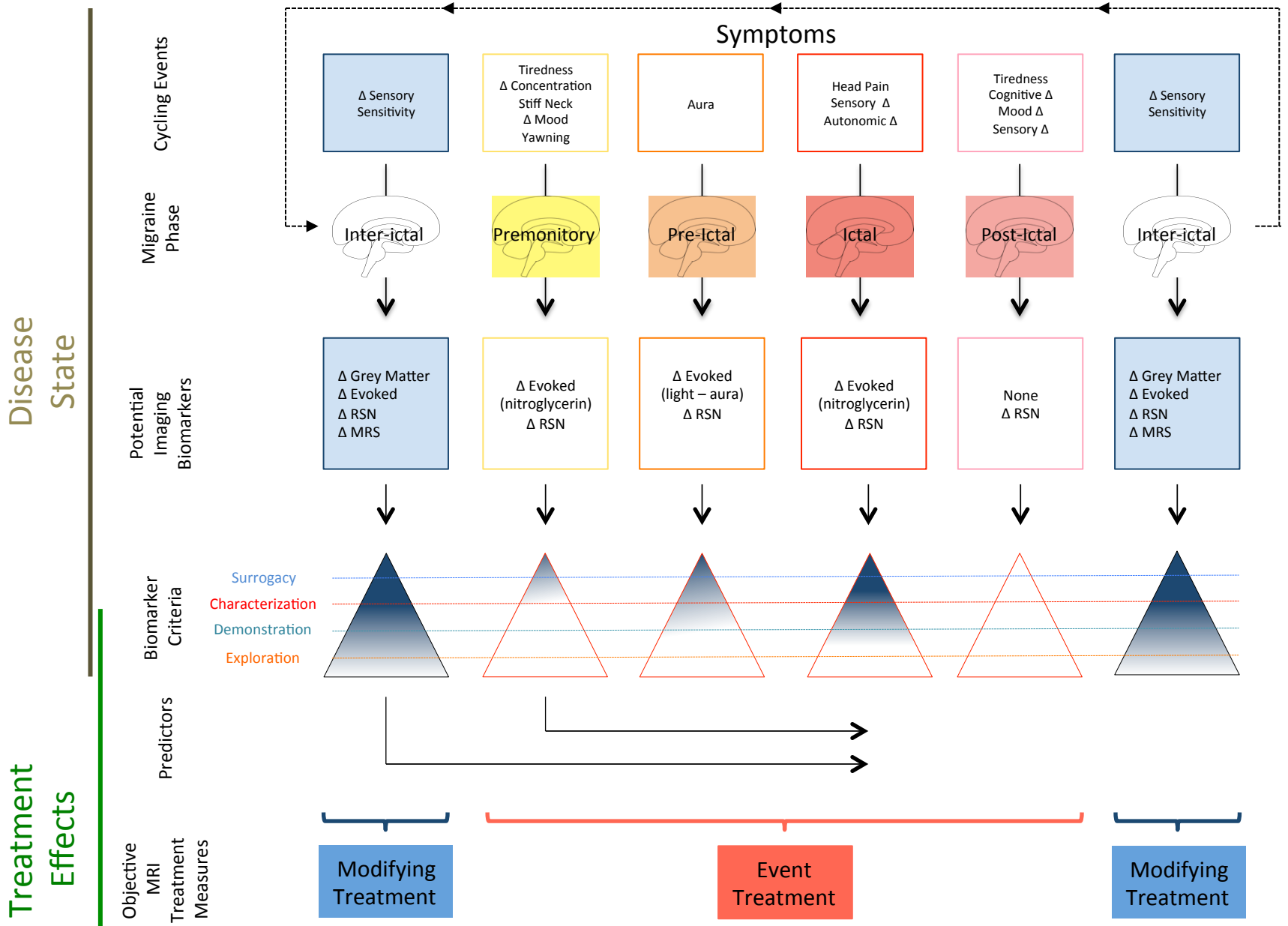
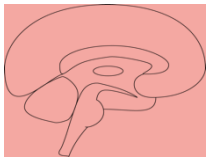


Figure 1: Migraine bio



Migraine Patient

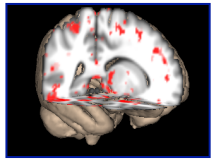
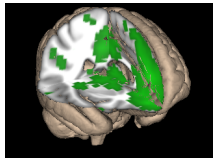
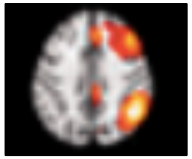
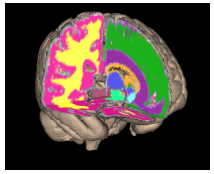
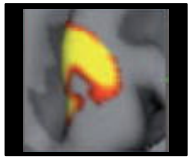
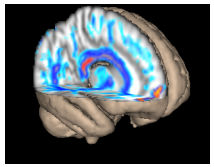
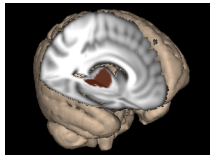
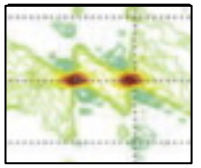
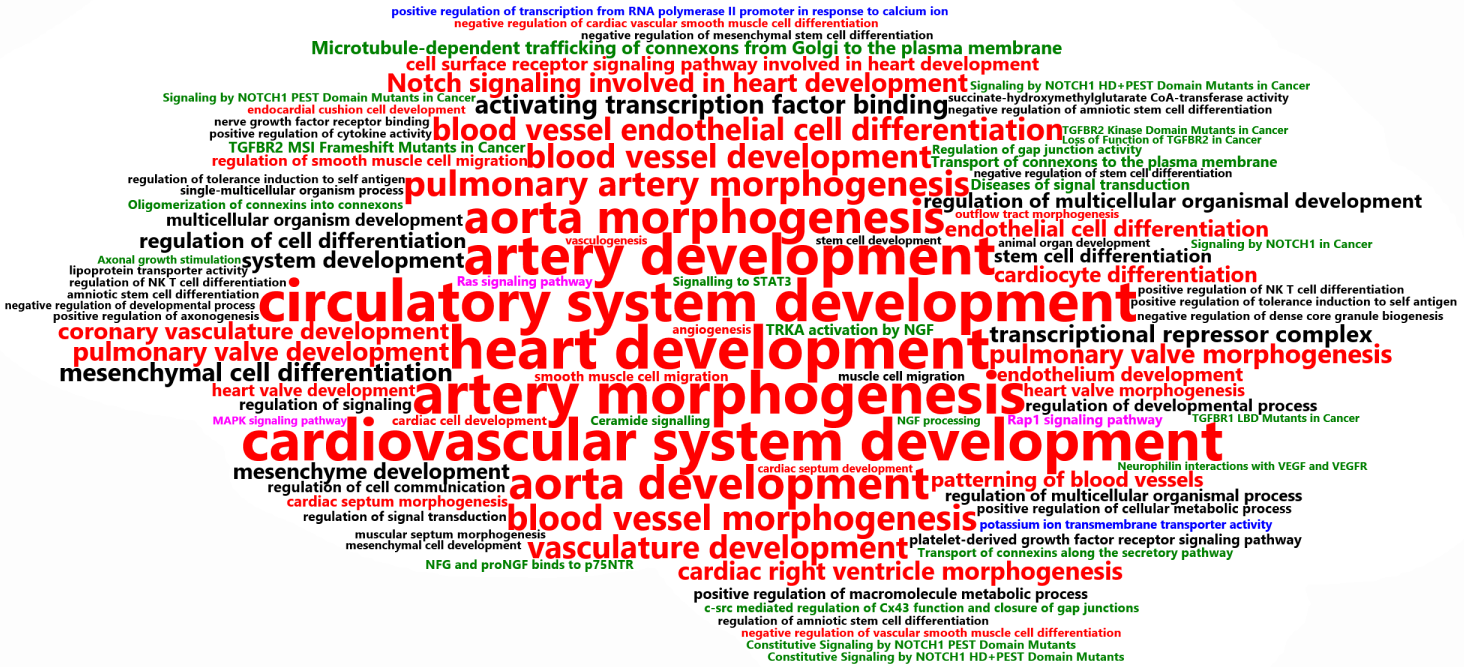
Imaging Approaches	Evaluative Data	Data Examples
BOLD fMRI 	A surrogate measure of neural function where cerebral blood flow correlates with neural activity. Studies usually employ evoked (psychological, pharmacological stimuli).	A 
RSN fMRI 	Resting state fMRI uses the same approach as BOLD to evaluate interactions (low frequency fluctuations) between different brain regions. Multiple RSN's exist.	B 
CT and VBM 	Measures of cortical thickness using MRI based techniques to define alterations in neuroanatomy (thickness/volume) with disease state or treatment effects.	C 
DTI 	An MRI approach to measure diffusion of water in white matter tracks that may be altered (architectural structure) in a disease state. Can also be used to map fiber tracts.	D 
MRS 	An NMR technique that measures brain metabolites (concentration or presence) eg., glutamate, GABA. It can also be used to evaluate neural integrity (NAA).	E 

Figure 2: Migraine Methods


positive regulation of transcription from RNA polymerase II promoter in response to calcium ion
negative regulation of cardiac vascular smooth muscle cell differentiation
negative regulation of mesenchymal stem cell differentiation
Microtubule-dependent trafficking of connexons from Golgi to the plasma membrane
cell surface receptor signaling pathway involved in heart development
Notch signaling involved in heart development
Signaling by NOTCH1 HD+PEST Domain Mutants in Cancer
Signaling by NOTCH1 PEST Domain Mutants in Cancer
activating transcription factor binding
succinate-hydroxymethylglutarate CoA-transferase activity
endocardial cushion cell development
negative regulation of amniotic stem cell differentiation
nerve growth factor receptor binding
blood vessel endothelial cell differentiation
TGFBR2 Kinase Domain Mutants in Cancer
positive regulation of cytokine activity
Loss of Function of TGFBR2 in Cancer
TGFBR2 MSI Frameshift Mutants in Cancer
Regulation of gap junction activity
regulation of smooth muscle cell migration
blood vessel development
Transport of connexons to the plasma membrane
negative regulation of stem cell differentiation
regulation of tolerance induction to self antigen
pulmonary artery morphogenesis
Diseases of signal transduction
single-multicellular organism process
Oligomerization of connexins into connexons
regulation of multicellular organismal development
aorta morphogenesis
outflow tract morphogenesis
multicellular organism development
endothelial cell differentiation
regulation of cell differentiation
vasculogenesis
stem cell development
animal organ development
Signaling by NOTCH1 in Cancer
artery development
Axonal growth stimulation
system development
stem cell differentiation
lipoprotein transporter activity
cardiocyte differentiation
regulation of NK T cell differentiation
Ras signaling pathway
Signalling to STAT3
positive regulation of NK T cell differentiation
circulatory system development
amniotic stem cell differentiation
positive regulation of tolerance induction to self antigen
negative regulation of developmental process
negative regulation of dense core granule biogenesis
positive regulation of axonogenesis
coronary vasculature development
angiogenesis
TRKA activation by NGF
transcriptional repressor complex
heart development
pulmonary valve development
pulmonary valve morphogenesis
mesenchymal cell differentiation
smooth muscle cell migration
muscle cell migration
endothelium development
heart valve development
artery morphogenesis
heart valve morphogenesis
regulation of signaling
regulation of developmental process
MAPK signaling pathway
cardiac cell development
Ceramide signalling
NGF processing
Rap1 signaling pathway
TGFBR1 LBD Mutants in Cancer
cardiovascular system development
cardiac septum development
Neurophilin interactions with VEGF and VEGFR
mesenchyme development
aorta development
patterning of blood vessels
regulation of cell communication
regulation of multicellular organismal process
cardiac septum morphogenesis
positive regulation of cellular metabolic process
regulation of signal transduction
blood vessel morphogenesis
potassium ion transmembrane transporter activity
muscular septum morphogenesis
platelet-derived growth factor receptor signaling pathway
mesenchymal cell development
vasculature development
Transport of connexins along the secretory pathway
NFG and proNGF binds to p75NTR
cardiac right ventricle morphogenesis
positive regulation of macromolecule metabolic process
c-src mediated regulation of Cx43 function and closure of gap junctions
regulation of amniotic stem cell differentiation
negative regulation of vascular smooth muscle cell differentiation
Constitutive Signaling by NOTCH1 PEST Domain Mutants
Constitutive Signaling by NOTCH1 HD+PEST Domain Mutants

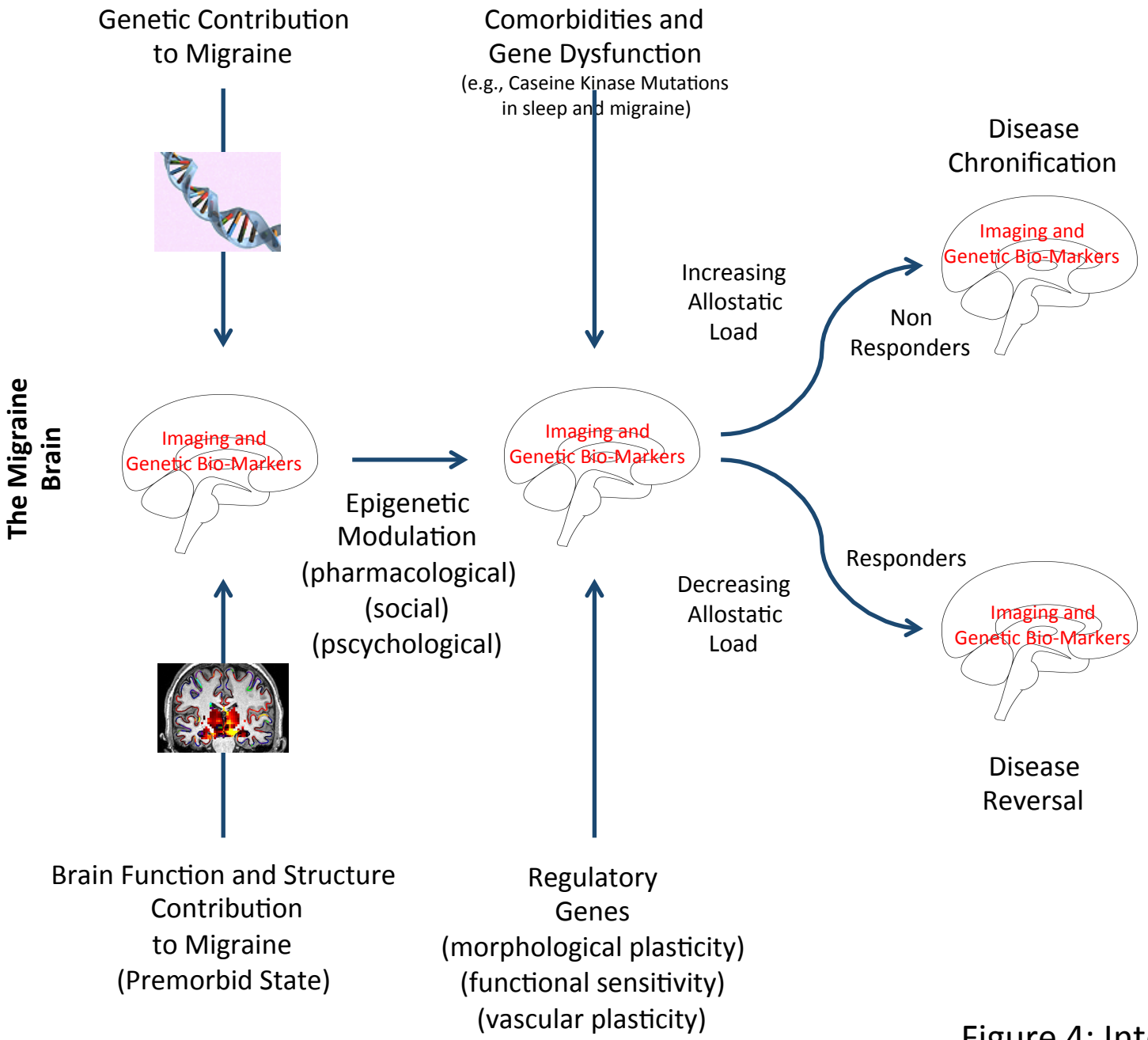


Figure 4: Integration