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Towards clinical applications of movie fMRI

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A B S T R A C T

As evidenced by the present special issue, movie fMRI is emerging as a powerful tool for exploring brain function and characterizing its variation across individuals. Here, we provide a brief perspective on the potential of movie fMRI for advancing the discovery of brain imaging-based markers of psychiatric illness. We discuss relevant gaps and opportunities in movie fMRI, and propose community-level models that might accelerate the pace of discovery of fMRI-based biomarkers in psychiatry.

1. Promise and utility

The use of movies as stimuli in fMRI research has expanded significantly since around 2004 when Hasson and colleagues first showed that BOLD-signal time-courses throughout large swathes of cortex were synchronized across subjects during movie-watching (Hasson et al., 2004). Interest in movies as neuroscientific stimuli has been fueled in part by the quest for more ecologically valid scanning conditions, and evidence suggesting that such conditions result in unique brain-based findings (Spiers and Maguire, 2007; Hasson et al., 2010; David et al., 2004; Sonkusare et al., 2019). For psychiatric imaging in particular, movie fMRI provides multiple advantages including: (i) the ability to drive higher-order neural processes; (ii) enhanced signal properties; and (iii) improved data quality and quantity.

It is hard to imagine a conventional fMRI task that could powerfully evoke attentional performance during complex social processing in attention-deficit hyperactivity disorder (ADHD), or a distorted sense of reality in psychotic illness, but the medium of film makes this possible (e.g., Rikandi et al., 2017; Salmi et al., 2019). For example, the Salmi article (this issue) shows that when watching a movie clip of a complex social conversation, no neural differences between ADHD and non-ADHD participants were observed. However, when relevant auditory distractors were overlaid onto the movie, ADHD-based neural differences were revealed. This is somewhat analogous to seeing a change in a patient's EKG (e.g., ST-segment elevation, which can indicate ischemic injury) while they are running that is not present while they are walking. In short, movies have the potential to be to the brain what running on a treadmill is to the heart during a cardiac stress-test: they could conceptually provide a standardized way to study the whole organ while it works, and in some cases could be used to compare function across different levels of intensity and demands. Much work, of course, remains to be done to define standard conditions and normative responses, and to quantify changes of "load" within a given movie, for a given participant, or for a particular symptom.

Movie-watching also confers advantages when it comes to signal properties that may be of particular help to biomarker research. Potential improvements in reliability—in part from improved participant engagement and compliance, and in part it seems, also due to the nature of the evoked signal itself—could provide a crucial increment of improvement when identifying clinically relevant differences in signal (O'Connor et al., 2017; Wang et al., 2017). Movie fMRI also enables researchers to avoid the confounds inherent to repetitions of stimuli needed with most conventional tasks (Hasson et al., 2010), while at the same time capturing signal variability that is relevant to development and behavior. Previous work shows that this variability can be missed when conventional task or resting-state conditions are used (Cantlon and Li, 2013; Vanderwal et al., 2019). Relatedly, movie fMRI enables us to capture brain dynamics under complex, more ecologically valid conditions. Such naturalistic dynamics may provide a new window into normal and abnormal brain function (Simony and Chang, 2019). Moreover,

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using movies preserves, and possibly amplifies, the ability to detect patterns of functional connectivity that are distinct at the individual level (Vanderwal et al., 2017). Finally, it is worth noting the potential value of movie fMRI to translational studies, where movies can serve as a common probe to link human and nonhuman brain function, going beyond what is possible with either resting state or the limited types of simple tasks that both nonhuman and human primates can perform with meaningful similarity (Mantini et al., 2012).

Finally, one of the more straightforward advantages of movie fMRI for psychiatric imaging is that using movies can improve data quality and quantity. Relative to resting state functional connectivity (RS-FC) and task-based fMRI, movie-watching has the potential to decrease boredom and repetitive behavioral demands, and to increase scanner tolerability. It may thus be particularly useful in populations that have difficulties limiting head motion during scanning (e.g., individuals with attention-deficit hyperactivity disorder), those who struggle with task performance (e.g., individuals with lower intellectual functioning) or staying awake (e.g., many psychiatric medications are sedating), as well as those who might feel especially anxious in the scanner. Scan duration is a crucial factor, and enabling longer functional runs by using movies may provide more reliable measures of FC, and enough data to support approaches such as functional hyperalignment (Conroy et al., 2013; Guntupalli et al., 2018; Nastase et al., 2019) and machine-learning. Further, it is easier to share movies across sites than it is a traditional task, potentially improving both generalizability and sample sizes (DuPre et al., 2019), though challenges achieving consistent stimulus presentation and accurate trigger, timing information and playback persist across both tasks and movies.

2. Gaps and opportunities

As with any nascent method, movie fMRI is rife with limitations and opportunities for innovation. Unlike tasks, and more similarly to rest, movies lack overt or built-in measures of task performance and attention. Fortunately, a growing number of non-disruptive solutions are possible, including in-scanner eye-tracking, Predictive Eye Estimation Regression (Son et al., 2019), intersubject correlations of BOLD-signal time courses in the frontal eye fields (Moraczewski et al., 2018), the use of physiological measures of arousal, and post-movie recall quizzes. Semi-disruptive measures, such as button pushes during a movie, are also possible, though the degree to which these interventions disrupt naturalistic processing and time courses is not yet clear. Other drawbacks inherent to movies that may be of particular concern in psychiatric imaging would be that movies are products (and reflections) of culture to a degree that most conventional tasks are not, which may hinder generalizability. Variation in the abilities needed to process movies (e.g., receptive language) may also pose a challenge for some studies. Further, it is not yet clear how viewing repetition might affect results (for example, in a treatment study), and whether such novelty effects need to be studied on a movie-by-movie basis.

Beyond these considerations regarding study design, many open questions remain about the analysis of movie-watching data. While traditional resting state analyses can be ported over to movie-watching data with minimal effort, these approaches likely miss or obfuscate movie-related signal change. Intersubject correlation is arguably the most popular movie-specific measure (Hasson et al., 2004; Jaaskelainen et al., 2008; Nummenmaa et al., 2018), but implementation varies as researchers attempt to optimize efficiency and address statistical nuances (Chen et al., 2019). Intersubject functional connectivity (ISFC) is another type of analysis that relies on stimulus-locked dynamics to uncover shared, stimulus-locked connectivity patterns (Simony et al., 2016). Researchers are beginning to address the challenge of achieving a rich level of stimulus annotation needed to facilitate model-based approaches (Bartels and Zeki, 2004; de la Vega et al., 2017; Häusler and Hanke, 2016; Lahnakoski et al., 2012; McNamara et al., 2017; Salmi et al., 2014). Further, though test-retest reliability data to date are promising, ongoing work is needed to test reliability of measures collected during different movies and in different populations. We are also just starting to investigate state-related changes in movies, and pressing questions remain about task-rest-movie differences, and also, movie-movie differences (Betti et al., 2013; Geerligs et al., 2015; O'Connor et al., 2017; Vanderwal et al., 2019). For example, it is not yet clear if/how discrete neural processes from particular tasks relate to the neural processing that occurs during movie-watching: To what degree is a movie simply just a sum of its task-parts? Do we first need to characterize cognitive states during movie-watching in order to usefully study connectivity during movie-watching?

3. Two models of movie-based biomarkers

Here, we identify two conceptual models for movie-based biomarkers and propose three strategies that could speed progress towards their identification (see Fig. 1). First, neuroimaging-based biomarkers in psychiatry may need to be identified in a piecemeal fashion, wherein a "golden triangle" is identified separately for each disorder (e.g., major depressive disorder) or symptom (e.g., anhedonia). The triangle would occur when brain measure A during movie B could identify risk for disorder/symptom C. Second, it would conceptually also be possible to create a rich assay of functional connectivity under naturalistic conditions (perhaps in combination with other states and tasks) and to combine this with a set of different probes (such as the analyses of certain networks) in the same data set. This could yield an index of standard brain measures, different patterns of which might be predictive of certain disease trajectories. An analogy here would be liver function tests, where different patterns of the same measures are diagnostically distinctive. *The challenge at this point for both models is multifold: how do we figure out how to obtain normative data for the most important brain measures under the optimal acquisition conditions?*

4. Accelerating the maturation of movie fMRI for psychiatry

4.1. Strategy 1: Movie fMRI in large-scale datasets

Efforts to eventually provide normative data during movie-watching will require large-scale datasets. While most ongoing large-scale studies are leveraging resting state and task fMRI, the Healthy Brain Network (Alexander et al., 2017) is an example of a psychiatrically-focused community imaging resource that has made the leap to movie fMRI (and movie EEG). Data from this database is featured in several manuscripts by different groups in the present special issue. Although focused on healthy adults, it is worth noting that the Human Connectome Project included movie fMRI on a subset of individuals. The Cam-CAN (Cambridge Centre for Ageing Neuroscience) dataset is also worth noting, as it spans adulthood (ages 8–88 years) (Shafto et al., 2014). For future large-scale datasets, we suggest that including a minimum of one movie run (minimum length: 10 min; optimal length: 25+ minutes) will vastly increase the types of analyses that can be conducted.

4.2. Strategy 2: Constraining the feature space with a priori networks

Identifying the most promising networks or regions to focus on for biomarker work using movies is especially challenging because of the rich feature space of movie-watching data. Here we propose the use of a priori information about human brain organization to provide a better feature-to-sample ratio. One way to achieve this is to use meta-analytically defined networks revealing the most likely location of the core nodes for a particular functional system (e.g., for the human self-regulatory system, see Langner et al., 2018), and then to focus on the within- or across-network interactions (Varikuti et al., 2018) during movie stimulation. In this context, one intriguing possibility is that different networks can be analyzed from the same data, and a priori network models function as probes or assays (Nostro et al., 2018;

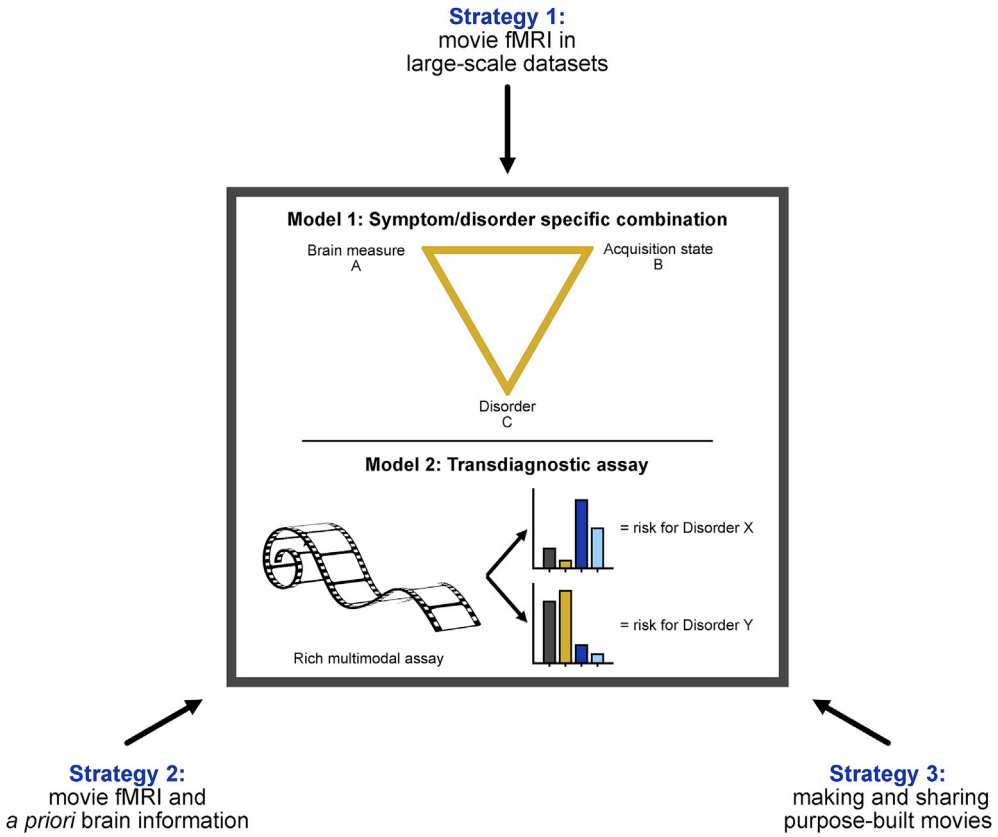

Fig. 1. Conceptual models for developing movie-based biomarkers, and community-based strategies to help accelerate progress of both models.

Pläschke et al., 2017). Hybrid approaches that leverage complementary strengths across paradigms are also useful (e.g., Ren et al., 2018). Alternatively, whole-brain parcellations (Schaefer et al., 2018) can provide a biological dimensionality reduction that allows researchers to train machine-learning models to predict phenotypes from region to whole-brain connectivity profiles (Chen et al., 2020; Weis et al., 2019). These methods, currently in use with resting-state data, could provide a critical link to understanding human brain organization during naturalistic conditions. Such efforts could lead to novel diagnostic tools that generalize to new subjects once sufficiently large movie datasets are available for machine-learning.

4.3. *Strategy 3: Making purpose-built movies*

Finally, identifying the optimal acquisition conditions for biomarker research using movies needs to be a communal undertaking, and we suggest that creating and sharing purpose-built movies will play an important role in these efforts. Some practical steps that might help guide efforts to compile a film library for fMRI studies would be to develop a list of "most needed" targets for movies (e.g., by disorder, symptom or network), and to have a website where researchers post their intention to make a particular movie. Perhaps most easily, a carefully selected or produced "kitchen sink" movie could become a common probe for multiple functions, including social cognition, language, emotions and memory (Sonkusare et al., 2019). Paradigms with greater and more widespread intersubject measures of both neural and physiological responses (in typical controls) might be a sensible place to start. Establishing a common multifaceted movie paradigm, even if done somewhat arbitrarily, may provide a foothold for identifying reliable and reproducible brain profiles within a field where current behavioral measures and diagnostic categories provide imprecise starting points.

Advantages to making our own movies include the ability to tailor content to specific questions, to dictate (and know) the stimulus properties up front, to embed task events within a naturalistic context, and to own the copyright to facilitate sharing of the stimuli. The drawbacks of movie-making for science include the substantial cost, effort and expertise involved. Movie-making is also risky insofar as there is no guarantee that a given film will evoke what it was designed to evoke, and in this sense, using a pre-existing Hollywood film may be advantageous. Sharing movies can justify the cost of making a purpose-built movie (e.g., *Inscapes*) (Vanderwal et al., 2015), and could also warrant rich phenotyping of the film, including comprehensive stimulus annotation, multi-site behavioral norming, and physiological characterization (e.g., eye-tracking, arousal dynamics). For example, the StudyForrest.org project is emerging as a community-focused effort on high dimensional annotation and characterization of a full-length film movie (Hanke et al., 2016; Häusler and Hanke, 2016). Overall, the cost, expertise and time needed to make movies for neuroscience warrant widespread sharing of these stimuli, and the complex, elusive properties of film as a medium make the sharing of movie-based paradigms essential from a science and reproducibility perspective.

5. Conclusions

In summary, movie fMRI is emerging as a promising tool for mapping and probing functional brain systems, especially in clinical populations. We have proposed two conceptual models of how movie fMRI-based biomarkers might work, namely, in a piecemeal fashion that is specific to each disorder or symptom, or via an assay of standardized brain measures that have utility across symptoms and disorders. Perhaps most importantly, recognizing the pressing need for clinically useful tools in psychiatry, we outlined three strategies for accelerating community-level progress in movie fMRI: developing largescale databases that include movies, picking regions and networks based on methods that can cope with the rich feature space of movie-watching data (e.g., meta-analyses or machine-based learning algorithms), and concerted, communal

efforts to arrive at useful, rigorously tested movie paradigms. It is our hope that collaboration and sharing on all three of these fronts will enable rapid delivery of the tools that our patients needed yesterday.

CRediT authorship contribution statement

Simon B. Eickhoff: Conceptualization, Writing - original draft, Writing - review & editing. **Michael Milham:** Conceptualization, Writing - original draft, Writing - review & editing. **Tamara Vanderwal:** Conceptualization, Visualization, Writing - original draft, Writing - review & editing.

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