Name, institution, and contact details of the applicant (one person only) and a list of the scientists or institutions involved in the research project (max. 2 A4 pages) CVs and lists of publications need not be submitted.

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INM-7: The proposed work is embedded in a multidisciplinary working team combining knowledge in the field of neuropsychology, structural and functional MRI analysis, computational neuroscience and machine learning.

Dr. Kaustubh Patil, head of the working group “Applied Machine Learning”

Rick Betzel is an associate professor at the Psychological and Brain Sciences Department of Psychological and Brain Sciences at Indiana University Bloomington, USA. He is an expert in principles of time-varying functional network reconfiguration and its relationship to ongoing cognitive processes and one of the developers of the edge time series approach which we will employ within the project suggested here.

Dynamic Cognition: Movies as a Window into Sex Differences in the Brain

Project Description

Background and Research Question

Functional brain imaging techniques, in particular fMRI have been widely used to investigate sex differences in the brain. Such differences in structural and functional brain organization play a crucial role in healthy human brain development, aging, as well as the manifestation of psychiatric and neurological disorders [2, 9]. Consequently, an understanding of sex differences in the human brain and their underlying mechanisms is critical for understanding both normative behavior and psychopathology.

In the present proposal, we aim to employ novel brain imaging methodology utilizing naturalistic viewing (NV), i.e. watching of Hollywood movies clips in the scanner, to broaden our knowledge of sex differences in the brain. While it is common knowledge that women and men often react differently to complex scenarios in films - think of how a couple might debate a movie's emotional impact after leaving the cinema - our study delves deeper than these everyday observations. Instead of relying on stereotypes such as 'women like emotional scenes, men like action', we will analyze in detail how brain activity and functional connectivity (FC) differs when women and men watch various movie scenes. This could reveal, for example, that women process subtle social cues in dialogues differently from men, while men might react more strongly to visual hints in action scenes that foreshadow danger. Through a thorough analysis of females' and males' brain responses to a variety of different movie scenes, we aim to develop a well-founded understanding of cognitive sex differences that advances our knowledge of sex differences in brain function beyond the current state of research.

So far, our understanding of sex differences in the brain is still far from complete. While there is some agreement on the existence of sex differences in specific cognitive domains like language and spatial processing, some researchers argue that female and male brains are altogether more similar than different [13] and that the overlap between the sexes is larger than their differences. Importantly, neuroimaging research on sex difference has so far only been able to capture certain aspects of these differences.

Classically, sex differences in the brain have been studied using task-based (TB) fMRI with tightly controlled tasks, offering insights limited to specific cognitive domains (e.g. [24, 27, 28]. However, due to the highly controlled and artificial nature of the tasks, ecological validity of task-related fMRI is usually very low and does not reflect cognitive sex differences as observed in daily life. More recently, resting state (RS) approaches have been employed, in which fMRI data is acquired while subjects relax in the scanner without any specific task demand or visual or auditory stimulation. Earlier RS studies examined group differences in connectivity patterns between women and men. More recently, however, machine learning (ML) methods have been applied to move beyond group averages: sex classification approaches use RS data to predict the sex of individual subjects and then infer which brain networks contribute most to distinguishing females from males. Using such an ML approach, we identified regionally specific brain networks that support successful classification, which, importantly, generalized from a training sample to an independent sample and revealed that predictive power—and thus cognitive sex differences—are most pronounced in higher-level cognitive regions involved in language, social cognition, and emotion processing [29, 31, 30].

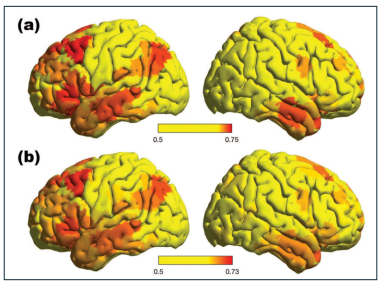

Fig. 1: ROI-based sex classification shows high accuracies for (a) within sample CV and (b) across sample classification.

Importantly though, RS fMRI only reflects the brain in a specific state, which has commonly interpreted as intrinsic brain organization and thus constitutes a trait rather than a state. Moreover, while a state of free mind wandering happens often in real life, what remains largely unexplored are sex differences in the "brain in action", i.e. when encountering complex, multimodal stimulation resembling real-life experiences. The present proposal aims to contribute to closing this gap in knowledge by applying the newly emerging NV approach to examine sex-specific brain responses in ecologically valid contexts. NV focuses on cognitive processes in dynamic, temporally extended, naturalistic contexts, which are much more akin to situations which the brain must deal with in real life. In NV tasks, participants in the scanner are presented with naturalistic material like movies. For the participants, there is no other task demand rather than watching the clips. NV offers an engaging task for the subject and thus avoids boredom in the scanner. Importantly, as opposed to RS, all participants are exposed to the same stimulus, for which content and timing is known and can be used in the analyses. NV approaches offer complex, dynamic and ongoing stimulation similar to experiences in everyday situations, where low-level (audiovisual) and high-level (cognitive and emotional) content

vary fluidly, creating a multimodal and immersive experience [23], offering the opportunity to capture dynamic neural processing in ecologically valid contexts [25]. Furthermore, NV has been shown to improve reliability and individual identifiability over RS [15] with a recent study from our lab [15] showing that the use of NV enhances the detection of FC patterns that are unique at the individual level.

Our lab pioneered NV analysis methods. We recently developed the topography-based predictive framework (TOPF) [17], which identifies individual-specific evoked activity topographies in a data-driven manner and examines their behavioral relevance using a ML predictive framework. TOPF effectively and stably captures individual differences in evoked brain activity and successfully predicts phenotypes across cognition, emotion and personality, and will be employed in the present context to uncover differences between females and males. In preliminary work using TOPF [17] on NV data, we achieved up to 80% accuracy in sex classification on single movie clips. Highly predictive regions were linked to emotion, language, and higher cognition. These promising findings await further validation over the course of the present project. Altogether, NV offers rich, time-evolving stimulation, allowing for the study of dynamic brain states across diverse scenarios. This method better reflects everyday cognitive and emotional challenges and may uncover novel sex differences in functional brain organization.

Surprisingly, to our knowledge, no study has yet used NV to systematically examine sex differences. In a previous publication [4], we have compared the potential of movies for the study of individual brain differences to what running on a treadmill is to the heart during a cardiac stress-test, i.e. to potentially provide a standardized way to study the whole organ while it works to compare function across different levels of intensity and demands. In the present context, this means that NV can be expected to reveal sex differences in the brain that so far have been unobservable, since NV data encompass an extensive range of dynamic real-life situations, such as social interactions, recognition of faces or perception of emotions [23]. While isolated cognitive processes as examined in TB fMRI might not reveal significant sex differences, the complex interplay of these processes - as engaged during movie watching - could highlight more pronounced differences between women and men. This underscores the value of using naturalistic stimuli to uncover subtle but meaningful variations in neural processing that might be missed in more controlled, simplified experimental paradigms. Using careful annotations of the movies, it is also possible to identify which features of a given scene are particularly relevant to evoking sex differences in complex experiences and to identify brain networks that differ most between females and males during these experiences.

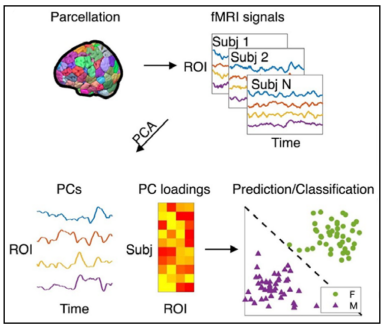

Fig. 2: TOPF captures individual differences in brain activity and successfully predicts phenotypes across cognition, emotion and personality.

We aim to employ novel methodology utilizing NV paradigms to expand our understanding of sex differences in the brain. This approach has the potential to elucidate sex-specific neural mechanisms in response to the complex and dynamic content of movies and to reveal nuanced sex-specific distinctions in brain function that may not be apparent in more constrained experimental paradigms or everyday observations. Our methodology leverages the ecological validity of movie stimuli to probe complex, multimodal cognitive processes in a controlled yet naturalistic setting. Through advanced neuroimaging techniques and sophisticated data analysis methods, we anticipate uncovering subtle yet significant sex-based variations in neural activity and FC that can inform our understanding of broader cognitive and behavioral differences between females and males. To this aim, we will first consider temporally aggregated FC evoked by movies over the duration of several minutes. Subsequently, we will further disentangle which specific events evoke sex differences and examine differences in the brain networks caused by such events. Furthermore, we will examine how the brain's response to the evolving narrative of the movies differs between the sexes. The project's comprehensive approach of examining temporally aggregated as well as time resolved FC, network dynamics and brain activity patterns provides a multi-faceted view of sex differences in the brain and, which can have implications for understanding sex differences in cognition, behavior, and susceptibility to certain neurological and psychiatric conditions.

Results from the proposed project have the potential to add a crucial new dimension to current knowledge on cognitive sex differences. Psychologically, these insights deepen our understanding of normative sex differences; clinically, they may help clarify why certain psychiatric and neurological disorders manifest differently in women and men. Such knowledge can potentially enhance diagnostic accuracy, inform personalized treatments, and support the development of sex-specific healthcare and education strategies.

Throughout the proposal, for ease of reading, the term "sex" will refer to the self-reported (biological) sex and appearance of the participants. At the same time, we fully acknowledge that "gender identity", i.e. the subjective identification of an individual as female, male, or one of the other gender identities which might be also fluid, also play important roles, which however, are beyond the scope of the present project.

Data: The Ju-MOVIES dataset

The work proposed here will be based on a data set that has already been acquired and is ideally suited for the examination of sex differences through a NV approach. Over the course of the project, further data will be collected. The paradigm comprises seven movie clips of about 8 - 10 minutes length, which are all excerpts from Hollywood movies ("Dirty Dancing", "Scream", "Dead Poets Society", "Forrest Gump", "Dead Man Walking", "Life is Beautiful", "The Good, the Bad, the Ugly"). The specific movie stimuli were chosen to cover a variety of social interactions and complex situations as well as multifaceted emotions evolving over the course of the movie to match the complex nature of real-life experiences. Considering that viewers lack the context of the entire movie, each stimulus was chosen to be long enough for the viewers to understand the situation, empathize with characters and follow the evolving narrative. Additionally, participants watch a compilation of 12 short movie clips ("Short Sequences"), which were again taken from Hollywood movies and completed two RS scans of about 9 minutes length with their eyes open.

So far, we collected data of 135 healthy participants (68 males, age 18 - 35 years, mean age = 24.33 years). All fMRI data are acquired on a Siemens 3T Prisma scanning (Siemens, Erlangen, Germany) with a 64-channel head coil at the Imaging Core Facility of Research Centre Jülich, using a T2w multiband echo planar imaging sequence with the following parameters: repetition time (TR) = 980ms, echo time (TE) = 30ms, flip angle = 70°, field of view (FOV) = 207 x 207mm, voxel size=2.2 x 2.2 x 2.0mm3, number of slices: 64, multiband acceleration factor=4, phase encoding direction=AP, FoV=207mm). A mirror fixed on the head coil allows participants to see a screen used to display the movies. In-ear headphones are used for ear protection and to deliver the movie sound. Additionally, a structural T1w image is acquired using an MP-RAGE sequence (TR=2000ms, TE=2.45ms, TI=900ms, flip angle=8°, FoV: 256mm) yielding 1mm3 voxels.

Saliva samples are collected from each participant and levels of cortisol, oestradiol, progesterone, and testosterone are analyzed by a specialized laboratory. Control for fluctuating hormone levels is essential for a meaningfully interpretation of potential sex differences in functional brain. Furthermore, data OC intake is noted for female participants. To characterize the movie stimuli in more detail, emotions perceived by viewers of the movies were assessed by 44 German participants (23 males, age 20-30 years, mean age 25.05 years) who watched all movie stimuli while simultaneously rating six basic emotions (happiness, fear, surprise, sadness, disgust and anger [5]). Rating were collected by the ReMoTa toolbox (Real-time Movie Tagging v0.0; [16]). Participants watched the movies on a laptop and rated their feelings by use of the keyboard. All emotions were rated simultaneously on a scale from 0 to 100 at a sampling rate of 10hz. The emotion ratings confirmed the multifaceted and diverse emotions elicited by the different movie stimuli. In a further annotation, two independent raters quantified the following features: faces, bodies, male / female presenting characters, ethnicity of characters, presence of children, adults, crowds, hands, buildings, vehicles, food, landscapes, animals, plants, movement, social interactions, place (inside or outside / urban vs. non-urban), time of day (day or night), weather, presence of music and camera movements.

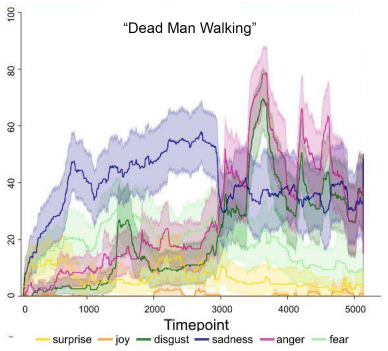

Fig. 3: Exemplary emotion annotation for one of the movie stimuli..

Work Program and Research Methods

The overarching goal of the proposed project is to complement existing research on sex differences by employing a NV approach. This method promises new insights into sex differences in the brain response to complex and dynamically evolving situations akin to what the brain has to deal with in real life. Results can go beyond existing studies based on both TB or RS approaches and promise novel insights that could so far not be achieved with existing research approaches. Specifically, we will examine which types of complex situations as depicted in the movie stimuli result in most pronounced sex differences. In the next steps, we will further disentangle which events within the movies' narrative drive these sex differences and examine how females' and males' brains respond differentially to the evolving narrative of the movies. We expect this novel approach to the study of cognitive sex differences together with the project's comprehensive approach of examining tem-

porally aggregated FC, event-related responses, network dynamics and brain activity as well as hormone related variability to provide important new insights into the multi-faceted spectrum of sex differences of the brain in action.

Firstly, in work package (WP) 1 we aim to go beyond existing results on sex differences in the RS by examining sustained FC over the course of a variety of movies of several minutes length. Using a temporally aggregated FC approach as commonly used for RS data, results of this WP will identify sex differences in "action brain states" and their underlying brain networks.

In WP 2, we will then employ a time resolved FC approach to identify temporally specific events driving sex differences in the experience of complex situations. This approach makes use of the know dynamics and content of the movies. Detailed annotations of the movie content will be used to characterize the type of situations that drive sex differences together with revealing sex specific cognitive strategies when encountering such situations.

In WP3, rather than looking at temporally aggregated or time resolved FC patterns we will examine the brain activation invoked by the movies. In particular, we will extract (within each brain region) typical female and male brain responses to the dynamically evolving movie content. This approach complements results from WP1 and WP2 through an understanding of how females' and males' brains respond differentially to the evolving narrative of the movies.

WP 1: The Brain in Action - The Naturalistic Viewing Action State (NV-AS)

Several studies have shown that sex classification based on RS FC can achieve high classification accuracies [3, 21, 29, 31, 30] by capturing temporally aggregated FC patterns evoked over a sustained state of free thought or mind wandering. Since these RS brain patterns are independent of any external stimulation, they are often taken as a proxy for intrinsic brain organization, and in that sense, constitute more of a trait rather than an actual state.

The present WP aims to supplement existing results on sex differences in the brain by examining temporally aggregated FC patterns induced by the complex narratives presented in the movies. In contrast to RS, we expect movie induced brain patterns to represent states that are strongly dependent on the content of the movies. As this content is known, it can be used to characterize evoked FC patterns and sex differences between them. Thus, in this WP we will consider sustained brain "action states" (ASs) evoked by different movies and compare sex classification accuracies based on different naturalistic viewing ASs (NV-ASs) to RS. Since sex differences in NV-ASs depend on movie content, annotations the content will be employed to characterize the evoked brain NS-ASs and sex differences between them. Thus, this WP will provide insights into which kind of situations evoke particularly prominent differences between females and males. Here, we are looking at sex differences in the overall experience of complex situations, which is different both from TB studies looking at sex differences within specific cognitive tasks and from RS which mostly reflects intrinsic brain organization. We assume, that putting the brain into action while experiencing different complex situations should bring out differences between females and males more strongly than unrestricted and thus uncontrolled free thought can [26].

To compare enduring NV-AS to RS and amongst different movies, we will employ a similar approach as in our previous work [29].

Briefly, after parcellating the fMRI data into non-overlapping parcels based on an established parcellation (e.g. [22]), a mean activation time course will be computed for each parcel and correlated with those of each of the other parcels. Then, for each parcel individually, the FC pattern with the rest of the brain will be used as features to train a sex classifier for which classification accuracy will be determined by use of a cross validation (CV) approach. This procedure results in a spatial map of sex classification accuracies across the brain for RS and each NV-AS (i.e. each movie). Importantly, and in contrast to the majority of previous studies, we will include hormone levels and OC status in women as confounds into all prediction analyses in WP1 to ensure that results delineate actual differences between the sexes, rather than hormone related variability. In doing so, we will take particular care to control for confound leakage [11], which might bias results of the prediction analyses.

WP 1.1: Comparing sex classification accuracies between RS and NV-ASs

As a first step, within each parcel, sex classification performance (across CV folds) will be compared between RS and NV-AS (averaged across all movies) by use of corrected resampled t-tests [19]. Higher classification accuracies during NV (compared to RS) will reveal cognitive sex differences that are specific to the brain in action rather than to its intrinsic organization. In addition, the spatial distribution of highly discriminative

parcels in NV will highlight the brain networks underlying these sex differences in the NV-AS. Cognitive domains related to the identified brain networks can be characterized by use of functional decoding [8]. While sex differences have often been reported in the DMN for RS [29, 32], for NV-AS, we expect sex differences in higher cognitive or task-general networks [12]. Furthermore, we expect sex classification based on NV-AS to outperform RS, as similar effects have been observed for other phenotypes [7, 26] and NV has been shown to increases individual identifiability over RS [15].

WP 1.2: Which movie features drive sex classification accuracies?

To further examine which kinds of complex situations maximize sex differences in the brain, we will characterize each movie clip by several visual and auditory features across the duration of the movie clips. These will comprise low-level features like mean motion energy, visual brightness and auditory loudness, high-level features like number of faces, social interactions and words, which can be automatically extracted [18, 20], and further movie features that have been acquired in our annotations. We will then compare sex classification accuracies across the whole brain between the eight different movies clips by use of a multiple regression approach, which will delineate which movie features drive classification performance for each brain parcel. As higher classification performance indicates more pronounced differences between the sexes, this procedure will result in a "movie feature profile" explaining which features of the movies result in most pronounced sex differences. By clustering brain parcels according to their movie feature profiles, we will identify brain networks in which sex differences are conjointly driven by specific features of the movies. We hypothesize that certain brain networks will comprise specific cognitive domains, in particular those that have been identified in classical group studies, which identified sex differences in cognitive domains like language and spatial cognition [10, 14]. Other networks can be expected to comprise more generalized and non-specific cognitive resources which are independent of the specific situation [12]. We expect domain-specific brain networks to overall achieve higher sex classification accuracies than domain-general networks. In an exploratory approach, we will compare the expressions of these networks in females and males by computing the first principal component of network FC patterns in females and males separately, thus identifying the "typical" female and male brain network pattern for each movie feature cluster. An exploration of these sex specific movie feature networks should help elucidate sex specific cognitive strategies in response to complex life-like situations.

Main Goal: Characterize sex differences in the NV-AS to reveal situationally modulated sex differences that may not be evident in RS.

Open Question: Will sex specific movie feature networks differ systematically, and what do these differences suggest about sex-specific cognitive strategies?

WP 2: Going dynamic: Sex differences in time-resolved FC

WP 1 will provide insights into sex differences in the overall NV-AS induced by different movies, thus identifying sex differences in brain networks evoked over the temporally aggregated state of perceiving a complex situation. However, one of the main advantages of using movies in the study of individual differences is that their content varies dynamically and that due to the shared stimulus experienced by all participants the impact of the dynamic movie content on the brain can be directly analyzed. Making use of this, the present WP will further disentangle the temporally aggregated FC pattern of the NV-AS into time resolved FC patterns at each time point of the movie. Going beyond characterizing "state type" movie content as a whole, here the main aim is to directly identify specific events within the movies that result in distinct time-point specific FC patterns that differ between females and males. These, in turn, can be further analyzed through the use of temporally resolved rather than movie wide annotations.

To achieve this goal, we will again parcellate the fMRI data and compute a mean activation time course for each parcel. Instead of considering the NV-AS, we will now decompose static FC patterns into moment-by- moment, single repetition time (TR) co-fluctuation patterns [1, 6]. Basically, the Pearson correlation which is above used as a measure of temporally aggregated FC between pairs of brain regions is "temporally unwrapped" by calculating the element-wise product of each pair of nodes' z-scored time series. For each edge, i.e. connection between two brain parcels, this results in a time series - typically referred to as "edge time series" (eTS) - representing the instantaneous co-fluctuation magnitude between the pairs, or simply speaking, the development of FC over time [1]. To identify dynamic FC differences between females and males during movie watching, we will identify time points within the movies, at which females' and malesÄ FC patterns are most distinct. To do so, we will employ a ML approach at each time point to classify sex based on the individual time resolved FC patterns. Given that the dimensionality of these features, i.e. the number of edges, is extremely high, we will

first employ a principal component analysis (PCA) for dimensionality reduction. Then, for each time point, the first n (e.g. 50) principal components will be used as features to train a sex classifier for which classification accuracy will be determined by use of a CV approach. Again, hormone levels and OC status will be included in the models as confounds to control for hormone related variability and possible confound leakage will be assessed and controlled for [11].

Using permutation tests we will identify those time points, for which classification accuracy differs significantly ($p < 0.05$) from chance, thus identifying events within each movie for which female and male time-resolved FC differs most. This approach offers the unique opportunity to link temporally specific sex differences in FC to movie content, thus identifying specific situations to which the sexes react differently. To characterize these situations, annotations of the movies will be used to identify movie events driving sex differences in time specific FC together with sex specific FC patterns driven by these features. To this aim, for each of the significantly different time points, the presence or absence of specific movie features (e.g. human bodies, faces, animals, scene cuts) will be coded binary, while continuous features (like luminance and audio level) will be coded as continuous numbers, thus creating a movie feature vector for each significant time point. We assume that typical sex differences in time resolved FC patterns will repeat across similar types of scenes in the different movies. Therefore, we will cluster the time points inducing significant differences between females and males according to their feature vectors, thus revealing parts of the movies that evoke sex difference during scenes with similar content. Then, for each of the time point clusters, we will compute a typical female and male FC pattern as the first component of a PCA across the FC patterns assigned to this cluster. This will identify typical female and male FC patterns in response to movies content associated with this cluster of movie scenes.

Finally, we will identify the pattern of brain regions that are most strongly involved in the typical female and male FC patterns for each cluster. Firstly, we will threshold the typical female and male FC patterns to identify most important edges in the sex-specific networks. Then, for each brain region, we will compute the weighted sum of all edges connected to that region and identify most important network nodes by selecting those for which summed FC strength exceeds the mean + 2 standard deviations across all nodes. This procedure will identify the sex specific spatial distribution of brain networks evoked by specific scenes in the movies.

Altogether, this procedure will shed light on which features within the movies induce most pronounced differences between females and males. Together with a set of features describing the movie scenes, we will identify female and male typical brain networks responding to these situations. While we expect to identify cognitive domains that match those identified in classical TB studies, the present approach will not only identify differences in specific isolated cognitive domains but reveal sex differences in cognitive strategies of dealing with certain complex situations. For example, while TB studies have identified sex differences in specific brain regions (like the fusiform face area) when participants viewed pictures of faces presented in isolation, our approach will depict sex differences in the brain when faces are encountered in a multimodal situation like in real life. Consideration of the brain networks evoked differently in females and males will shed light on sex specific neuronal patterns in perceiving faces.

Main Goal: Identify temporally specific movie events driving sex differences in the experience of real life- like stimuli and related differences in time-resolved FC patterns.

Open Question - Relation to Classical Findings: How do naturalistic sex differences observed here relate to findings from traditional TB paradigms (e.g., isolated face viewing)? Are the same brain regions implicated, or do new networks emerge under ecologically valid conditions?

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