

## Characterizing *Inscapes* and resting-state in MEG: Effects in typical and atypical development

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### ABSTRACT

Examining the brain at rest is a powerful approach used to understand the intrinsic properties of typical and disordered human brain function, yet task-free paradigms are associated with greater head motion, particularly in young and/or clinical populations such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). *Inscapes*, a non-social and non-verbal movie paradigm, has been introduced to increase attention, thus mitigating head motion, while reducing the task-induced activations found during typical movie watching. *Inscapes* has not yet been validated for use in magnetoencephalography (MEG), and it has yet to be shown whether its effects are stable in clinical populations. Across typically developing ( $N = 32$ ) children and adolescents and those with ASD ( $N = 46$ ) and ADHD ( $N = 42$ ), we demonstrate that head motion is reduced during *Inscapes*. Due to the task state evoked by movie paradigms, we also expectedly observed concomitant modulations in local neural activity (oscillatory power) and functional connectivity (phase and envelope coupling) in intrinsic resting-state networks and across the frequency spectra compared to a fixation cross resting-state. Increases in local activity were accompanied by decreases in low-frequency connectivity within and between resting-state networks, primarily the visual network, suggesting that task-state evoked by *Inscapes* moderates ongoing and spontaneous cortical inhibition that forms the idling intrinsic networks found during a fixation cross resting-state. Importantly, these effects were similar in ASD and ADHD, making *Inscapes* a well-suited advancement for investigations of resting brain function in young and clinical populations.

### 1. Introduction

Examining the brain at rest has proven to be a powerful approach to understanding the intrinsic functional properties of the human brain. After establishing that activity in the resting brain is not noise, but highly structured spontaneous activity (Biswal et al., 1995), research has focused on resting-state networks: sets of spatially distributed yet temporally correlated brain regions which are functionally connected at all times (Deco and Corbetta, 2011; Raichle, 2011). Despite the absence of a task, the brain has still been shown to be highly dynamic during periods of rest (Kucyi, 2018). The characteristics of these networks in typical individuals has been classically investigated using functional magnetic resonance imaging (fMRI) (see van den Heuvel and

Hulshoff Pol, 2010 for a review), but have since been extended to other neuroimaging modalities such as magnetoencephalography (MEG) (Brookes et al., 2011).

A key benefit in using resting-state to investigate functional connectivity, in contrast to traditional task-based or stimulus-driven paradigms, is the ability to collect usable data on a broader sample of participants. Since task-based paradigms can be too difficult for many patient and paediatric populations to perform in the neuroimaging environment, such studies are often unfortunately limited to high functioning, older individuals who are able to participate (Gaillard et al., 2001; Greicius, 2008), and thus not representative of the full clinical sample. In contrast, during resting-state acquisitions, participants are normally

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asked to remain awake while keeping their eyes open, and often presented with a fixation cross on which to focus. Task-free resting-state is not limited by performance ability and is more easily acquired in young children and clinical populations such as autism spectrum disorder (ASD), and attention-deficit/hyperactivity disorder (ADHD).

Despite its advantages, task-free neuroimaging paradigms still suffer from the same caveat as their task-based counterparts: motion. In fact, Huijbers and colleagues have reported increased head motion during resting-state compared to task conditions (Huijbers et al., 2017). Head motion has become a prominent concern in neuroimaging, as even minimal amounts can result in spurious yet systematic and spatially structured patterns of brain activity in fMRI (Power et al., 2012) and inaccurate localization of brain activity in MEG (Wehner et al., 2008). Addressing head motion is of particular importance when performing developmental studies, since head motion is positively correlated with age over childhood (Satterthwaite et al., 2012) and group, when investigating clinical populations, who move more than control participants (Couvry-Duchesne et al., 2016; Yerys et al., 2009). Considerable effort has been devoted to developing adequate data processing strategies to control for head motion after data acquisition in fMRI (Power et al., 2015, 2014) and MEG (Messaritaki et al., 2017; Stolk et al., 2013). Minimizing motion during the time of acquisition, however, is superior to trying to correct for its effects afterwards and would further bolster resting-state as an advantageous technique to study neurodevelopment and clinical populations.

Many have examined neural activity while watching a movie (Hasson et al., 2010; Spiers and Maguire, 2007), which has been found to increase participant compliance, decrease motion, prevent sleep and provide a higher test-retest reliability compared to fixation cross resting-states (Greene et al., 2018; Power et al., 2012; Raschle et al., 2009; Vanderwal et al., 2019, 2017, 2015). However, despite being able to measure the brain's intrinsic functional connectivity during movie watching as seen during true resting-states, movies have been shown to evoke their own task-induced brain responses to the social and verbal nature of movies, which are dependant on the chosen movie and participant engagement (see Vanderwal et al., 2019, for review). Thus, to suppress these responses and increase the ability to measure intrinsic functional connectivity while still leveraging the decreased head motion advantage provided by movies, Vanderwal et al. developed a non-social and non-verbal movie paradigm called *Inscapes* (Vanderwal et al., 2015), which consists of slowly moving abstract shapes with a gentle piano score. In typically developing (TD) children and adults, *Inscapes* has been found to decrease head motion during fMRI data acquisition compared to both movies and fixation cross, maintain the improved ability to detect an individual's unique functional connectivity patterns seen in movies compared to rest, and produce functional connectivity patterns more similar to rest than movies (Vanderwal et al., 2017, 2015). *Inscapes* has also been successfully used in fMRI studies on TD preschool (Blankenship et al., 2019) and school-aged (Blankenship et al., 2019; Geng et al., 2019; Xiao et al., 2019) children and low-functioning children with ASD (Gabrielsen et al., 2018). Natural viewing conditions have also been shown to increase test-retest reliability using fMRI (Wang et al., 2017), which is a particularly important feature when attempting to establish biomarkers for clinical populations or performing longitudinal analyses. A recent study using electroencephalography (EEG) found that alpha/beta event-related desynchronization (ERD) was stronger during movie watching compared to rest, with the degree of ERD during *Inscapes* falling between traditional movies and rest (Espenhahn et al., 2020). However, to date, there have been no studies using *Inscapes* with MEG, nor any studies validating whether the observed effects of using *Inscapes* versus resting-state paradigms in typical participants are consistent with those observed in clinical populations.

MEG measures electrophysiological signals that directly reflect neuronal activity and provides a comparable spatial yet far superior temporal resolution compared to fMRI, which only indirectly measures neural activity through hemodynamics. Despite there being no stud-

ies using *Inscapes* with MEG, several studies have investigated the effects of viewing movies using MEG in adults. Movies have been shown to produce consistent inter-subject correlations in sensory regions using MEG (Chang et al., 2015; Lankinen et al., 2018) which are more pronounced at lower frequencies ( $< 10$  Hz) (Lankinen et al., 2014). Betti et al. (2013) found that the topography of resting-state functional connectivity in adults was stable between movie-watching and fixation cross resting-state in both fMRI and MEG. However, alpha and beta band limited power connectivity was decreased to movies in MEG compared to fixation cross within and across classic resting-state networks, extending their findings to time-scrambled versions of the movies (Betti et al., 2018). No study has examined the effect of using movies or *Inscapes* in TD children using MEG.

By reducing head movement, *Inscapes* has the potential to enable the acquisition of higher quality imaging data in children with neurodevelopmental disorders, which would lead to fuller understanding of the dysregulated neurobiology underlying these disorders and how maladaptive trajectories unfold across development. Behaviourally, ASD has been associated with hypo- and hyper-sensitivity to sensory stimuli (Ben-Sasson et al., 2009); however, those diagnosed with ADHD, which has a high co-occurrence rate with ASD, have also been reported to experience sensory sensitivities (Ghanizadeh, 2011). Atypicalities in resting-state MEG functional connectivity have been reported in ASD (e.g., Cornew et al., 2012; Kitzbichler et al., 2015; Tsiaras et al., 2011) and ADHD (Franzen et al., 2013; Khadmaoui et al., 2016; Wilson et al., 2013). Thus, since *Inscapes* provides a substantially different sensory experience compared to fixation cross resting-state paradigms, where atypicalities have already been reported, it is important to identify potential interactions in functional connectivity between these disorders and TD controls with *Inscapes* and fixation cross resting-states so results can be interpreted appropriately.

In the current study, we compared the effects of using *Inscapes* versus a fixation cross resting-state across typically developing (TD) ( $N = 32$ ) children and adolescents and those with ASD ( $N = 46$ ) or ADHD ( $N = 42$ ) between 5 and 19 years of age using MEG. We examined the intrinsic properties of neural functioning at a regional and network level using power spectral density (PSD) and functional connectivity measured using both amplitude envelope and phase-based measures on a spectral level. Neuronal processes are driven by both the phase and amplitude of the underlying oscillations, and connectivity arising from these constructs is thought to differ in their origins, structure and function (Engel et al., 2013). Given the known role of alpha oscillations in sensory gating and inhibition, we hypothesized that alpha activity would be suppressed during visual stimulation (e.g. *Inscapes*) extending previous studies reporting modulation between rest and movie watching (Betti et al., 2018, 2013). Furthermore, we predicted a network-level effect in three networks in particular - the visual network due to the additional sensory processing induced by *Inscapes* images; the default mode network (DMN), the cortical core of dynamic network toggling that is engaged at rest, but disengaged during task paradigms (de Pasquale et al., 2012; Raichle, 2015); and the dorsal attention network, which is responsible for maintaining the attentional focus (Corbetta et al., 2008) and is closely related to the default mode network (Toro et al., 2008). However, the visual, default mode and attention networks dynamically engage and disengage with other intrinsic resting-state networks, such as the motor, language and salience networks, and thus were also explored. We then examined potential group-by-condition interactions between the three diagnostic groups.

## 2. Methods

### 2.1. Participants

One hundred and eighty-five children between five and 19 years of age were recruited who were part of the larger Province of Ontario Neurodevelopmental Disorders (POND) network, a research collaboration

across institutions in Ontario, Canada. Study protocols were approved by the Research Ethics Boards of the participating institutions. Participants provided informed consent or, where appropriate, informed assent with consent provided by a guardian. Participants either demonstrated typical development (TD;  $N = 45$ ), reflecting absence of prematurity and neurodevelopmental, psychiatric and neurological disorders, or received primary clinical diagnosis of ASD ( $N = 71$ ) or ADHD ( $N = 69$ ). ASD diagnoses were based on expert clinical judgement, confirmed using the Autism Diagnostic Observation Schedule-2 (Lord et al., 2012) and Autism Diagnostic Interview-Revised (Lord et al., 1994); ADHD diagnoses were confirmed with the Kiddie Schedule for Affective Disorders and Schizophrenia (Kaufman et al., 1997) and Parent Interview for Child Symptoms (Ickowicz et al., 2006). Furthermore, all children were free of contraindications for MEG and MRI.

Full-scale IQ was obtained using age-appropriate Wechsler scales of intelligence (Wechsler, 2014, 2012, 1999; Weschler, 2003). The Child Behaviour Checklist attention problem subscale (CBCL-AP; Achenbach and Rescorla, 2001) was also administered to capture a measure of inattention characteristic of ADHD, yet also expressed in those with ASD. The Social Communication Questionnaire total score (SCQ-TOT; Berument et al., 1999) was used to capture of a measure of social communication problems characteristic of ASD, yet also present in those with ADHD. Finally, the Adaptive Behaviour Assessment System's General Adaptive Composite score (ABAS-GAC; Harrison and Oakland, 2003) was used to capture a measure of the general adaptive function deficits found in both neurodevelopmental disorders.

## 2.2. Data acquisition

Five-minutes of eyes-open data were acquired while the participants were positioned supine, for each of the two viewing conditions: fixation cross resting-state and *Inscapes*. For the fixation cross resting-state, participants were instructed to fixate on a grey cross centrally positioned within a grey circle on a black background. For the *Inscapes* recording, the first five minutes of the movie was played with the accompanying piano score. The two scans were completed in pseudo-random order across participants and groups. MEG data were continuously recorded (600 Hz sampling rate) using a 151-channel CTF system (CTF MEG International Service Ltd., Coquitlam, British Columbia, Canada) within a magnetically shielded room. The fixation cross and *Inscapes* were back projected onto a screen inside the magnetically shielded room, positioned approximately 70 cm from the participant's eyes; the piano score was played over speakers in the imaging suite. A third-order spatial gradient was used to improve signal quality with a 0–150 Hz recording bandpass for anti-aliasing. MRI T1-weighted anatomical images were also obtained on each participant to allow for subject-specific head models. The T1-weighted images were acquired using a 3T MAGNETOM Siemens PrismaFIT scanner with a 20-channel head and neck coil (TR/TE = 1870/3.14 ms, FA = 9°, FOV = 240 × 256 mm, # slices = 192, resolution = 0.8 mm isotropic). Prior to MEG data acquisition, children were fitted with fiducial coils placed at the left and right preauricular points and nasion to continuously track head location during recordings. Upon completion of MEG data acquisition, the fiducial coils were replaced with radio-opaque markers prior to the MRI scan to enable coregistration between the MEG and MRI data. Raw data used in the current study is currently in the process of being made available via a public repository, Brain-CODE (Vaccarino et al., 2018).

## 2.3. MEG preprocessing

Fixation cross resting-state and *Inscapes* data were preprocessed using the FieldTrip software toolbox (git commit 4c12371; Oostenveld et al. 2011). Data were bandpass (1–150 Hz, 4th order two-pass Butterworth filter) and notch filtered (60 and 120 Hz, discrete Fourier transform). The data were divided into 10 s epochs, and independent component analysis (fastica) was used in FieldTrip to identify eye move-

ments and cardiac artefacts, which were subsequently removed from the data. Epochs where head movement exceeded 10 mm from the segment's median head position were excluded, a threshold chosen to conform with previous paediatric MEG studies (Doesburg et al., 2013; Pang, 2011; Safar et al., 2018); epochs with MEG sensor signals exceeding 2000fT were also dropped. Participants were required to have at least one minute of data (6 epochs) remaining in both datasets to be included in the subsequent analyses. After recording the number of epochs remaining for each participant and the mean head motion across these epochs, excess epochs were dropped to match between fixation cross and *Inscapes*; mean head motion was then re-calculated across the remaining epochs. Note that epochs were dropped to ensure no significant differences in the number and mean head motion of those remaining between groups or resting-state post-matching.

We investigated the effect of fixation cross resting-state versus *Inscapes* on seven brain networks: dorsal attention, ventral attention, default mode, visual, motor, language and salience. To do so, we identified the centroid coordinates of 48 regions associated with these networks in MNI space. Centroids for the regions comprising the dorsal attention, ventral attention, default mode, visual, motor and language were extracted from de Pasquale et al. (2012), while regions comprising the salience network were identified via Brier et al. (2012). Regions included in each network are summarized in Supplemental Table 1, and visually presented in Supplemental Fig. 1. Each participant's anatomical MRI image was used to warp the 48 sources from MNI space into subject-MRI space. The timeseries for each of the source locations were reconstructed for each epoch using the FieldTrip implementation of the linearly constrained minimum variance beamformer (Van Veen et al., 1997). To define the forward model, the MRIs were used to construct subject-specific single-shell head models (Nolte, 2003) which were coregistered to the MEG data using the fiducial points. Covariance matrices were calculated within a broadband (1–150 Hz) covariance window across the entire dataset with 5% Tikhonov regularization. The forward model and covariance matrices were used by the LCMV beamformer to estimate a spatial filter to derive a timeseries for each source. The LCMV beamformer outputs were normalized by the estimated noise to correct for centre-of-head biases.

## 2.4. Power spectral density

After z-scoring the epoch-wise regional time courses for each viewing condition to account for variable between-subject amplitudes, Welch's method was used to estimate power spectral density (PSD) implemented in MATLAB (The Mathworks Inc., 2016; "pwelch" function: <https://www.mathworks.com/help/signal/ref/pwelch.html>). For each region, PSD was averaged across epochs and divided into five canonical frequency bands: theta (4–7 Hz), alpha (8–14 Hz), beta (15–29 Hz), low gamma (30–55 Hz), and high gamma (65–80 Hz). Each participant's data were then averaged over each frequency band to obtain a frequency-specific regional PSD estimate for each viewing condition.

## 2.5. Connectivity

The epoch-wise regional time courses for each viewing condition were also filtered into the five canonical frequency bands using a two-pass FIR bandpass filter designed using the Hamming window with the *fir1* function in MATLAB (The Mathworks Inc., 2016). To measure phase synchrony between pairs of regions, the weighted phase lag index (wPLI; Vinck et al., 2011) was used, which measures the consistency of the lag between two signals, attenuating phase angle differences around 0° or 180° that might be driven by volume conduction, beamformer leakage, or putative 'ghost' interactions (Palva et al., 2018). After applying the Hilbert transform, the instantaneous phase was used to extract epoch-wise wPLI values between 0 and 1 for each pair of regions, where a value of 0 indicates no phase locking or synchronization between the

regions while a value of 1 indicates full phase-locking or synchronization between the regions; resulting values were averaged across epochs. To measure amplitude envelope correlations, instantaneous amplitude envelope data were first corrected for signal leakage using a symmetric orthogonalization procedure (Colclough et al., 2015). The Hilbert transform was used to extract the instantaneous amplitude and amplitude envelope correlation (AEC) was calculated by computing the Pearson correlation coefficient between each pair of brain regions across each epoch. This resulted in a wPLI and AEC connectivity matrix for each subject, frequency band and viewing condition. Resulting connectivity matrices were summarized into within- and between-network connectivity by averaging over connections belonging to each network and belonging to each pair of networks, respectively.

## 2.6. Statistics

To test for differences in age, IQ, CBCL-AP, SCQ-TOT, and ABAS-GAC amongst the three diagnostic groups (TD, ASD, ADHD), one-way ANOVAs were performed. If significant, post-hoc analyses were performed using Tukey-Kramer tests to determine which groups were driving the significant effects. A chi-squared test was performed to test for a difference in the proportion of males and females amongst the three groups, followed by post-hoc pairwise chi-squared tests upon significance. In all cases, significance was held at  $p < 0.05$ .

To examine the effects of viewing condition, group and their interaction on the number of epochs surviving the rejection criteria, a repeated measure ANOVA was performed; upon significance of a group effect or group-by-condition interaction, post-hoc Tukey-Kramer tests were performed. An identical procedure was used to examine the effects on mean head motion across the included epochs. After matching the number of epochs between the fixation cross resting-state and *Inscapes*, a one-way ANOVA was performed to ensure no significant effect of group, and a repeated-measures ANOVA was performed to ensure there was no significant effect of viewing condition, group and their interaction on the mean head motion across the matched epochs.

For each viewing condition and frequency, the PSD data for each region were averaged across each resting-state network. For each frequency band, the resulting data were submitted to repeated-measures ANOVAs to examine the main effects of viewing condition and diagnostic group on each network and their interaction, controlling for age;  $p$ -values were Bonferroni-corrected to control for multiple comparisons across the seven networks, and significance was held at  $p_{\text{corr}} < 0.05$ . Upon significant main effects of age, Pearson correlation coefficients ( $R$ -values) were computed to determine the directionality of the effects. An identical procedure was performed to investigate differences between fixation cross and *Inscapes* in the within- and between-network wPLI and AEC connectivity;  $p$ -values were Bonferroni-corrected to control for the multiple comparisons across the 28 comparisons (7 within-network and 21 between-network).

## 3. Results

### 3.1. Participant demographics

After removing 65 participants who failed to meet the inclusion criteria, 32 typically developing (5 – 19 years,  $M_{\text{age}}=11.8$ ,  $SD=4.2$ , 24 males), 42 ADHD (6 – 16 years,  $M_{\text{age}}=11.5$ ,  $SD=2.7$ , 30 males), and 46 ASD (7 – 17 years,  $M_{\text{age}}=12.9$ ,  $SD=3.1$ , 33 males) children remained. A one-way ANOVA revealed no significant difference amongst the groups in age ( $F(2, 117)=2.23$ ,  $p = 0.11$ ), and a chi-squared test revealed no significant difference amongst the groups in the proportion of males and females ( $\chi^2(2)=0.14$ ,  $p = 0.93$ ).

### 3.2. Behavioural measures

Amongst the three groups, there was a significant difference in IQ ( $F(2, 117)=6.34$ ,  $p = 2.55 \times 10^{-3}$ ), which was driven by a significantly higher IQ in the TD compared to ASD children ( $p = 2.28 \times 10^{-3}$ ). A significant difference was also found in attention problems (CBCL-ADHD;  $F(2, 117)=47.74$ ,  $p = 1.40 \times 10^{-15}$ ), with both ASD ( $p = 9.81 \times 10^{-10}$ ) and ADHD ( $p = 9.56 \times 10^{-10}$ ) children having significantly worse scores compared to the TD children, and ADHD children scoring worse than ASD children ( $p = 0.03$ ). There was also a significant difference in social communication skills (SCQ-TOT;  $F(2, 117)=95.77$ ,  $p = 1.19 \times 10^{-24}$ ), with all three post-hoc tests being significant: ASD children showed significantly worse social communication deficits than both ADHD ( $p = 9.56 \times 10^{-10}$ ) and TD ( $p = 9.56 \times 10^{-10}$ ) children, and ADHD children also scoring significantly worse than those with TD ( $p = 0.01$ ). Similarly, the three groups showed a significant difference in general adaptive functioning (ABAS-GAC;  $F(2, 117)=46.05$ ,  $p = 5.17 \times 10^{-15}$ ), with the ASD children having greater difficulties compared to the ADHD ( $p = 4.22 \times 10^{-6}$ ) and TD children ( $p = 9.56 \times 10^{-10}$ ), and the ADHD children also scoring significantly worse than the TD ( $p = 7.21 \times 10^{-5}$ ). Descriptive statistics and statistical results for the behavioural measures are summarized in Table 1.

Across all three diagnostic groups, a repeated measure ANOVA revealed a significant effect of group ( $F(2, 117)=3.33$ ,  $p = 0.04$ ) and condition ( $F(1, 119)=33.92$ ,  $p = 5.15 \times 10^{-8}$ ) on the number of epochs prior to matching; there was no significant group-by-condition interaction ( $F(2, 117)=0.14$ ,  $p = 0.87$ ). Furthermore, a repeated measure ANOVA revealed a significant effect of condition ( $F(1, 119)=28.52$ ,  $p = 4.61 \times 10^{-7}$ ) on the mean head motion; there was no significant effect of group ( $F(2, 117)=2.51$ ,  $p = 0.09$ ) nor group-by-condition interaction ( $F(2, 117)=1.01$ ,  $p = 0.37$ ) on mean head motion. After matching, a one-way ANOVA confirmed that no significant effect of group on the number of epochs remaining ( $F(2, 117)=2.11$ ,  $p = 0.13$ ), and a repeated measures ANOVA revealed no significant effects of group ( $F(2, 117)=1.74$ ,  $p = 0.18$ ), condition, ( $F(1, 119)=3.24 \times 10^{-3}$ ,  $p = 0.95$ ), nor group-by-condition interaction ( $F(2, 117)=1.98$ ,  $p = 0.14$ ) on mean head motion. Descriptive statistics and statistical results for the viewing condition behavioural measures pre- and post-epoch matching are summarized in Supplemental Tables 2 and 3, respectively, and in Fig. 1.

### 3.3. MEG analyses

#### 3.3.1. *Inscapes* versus fixation cross

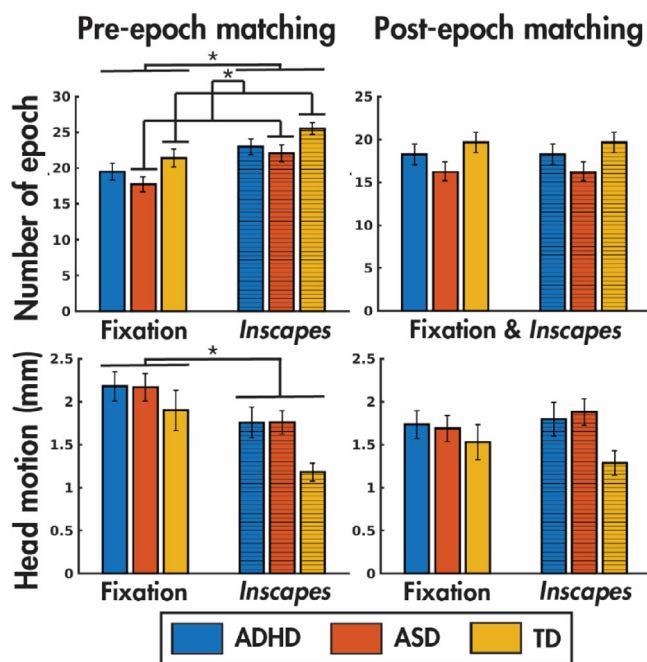
Across the ASD, ADHD and TD participants, main effects of viewing condition on PSD were found in all five frequency bands (Fig. 2A). In all bands except for alpha, PSD was higher during *Inscapes* compared to fixation cross, while in alpha, the opposite effect was found. Alpha band power is inversely related to cortical excitability, and reduced alpha power is associated with increased visual attention (Rajagovindan and Ding, 2011) and a release from gating through inhibition (Jensen and Mazaheri, 2010); thus, across all bands and networks, local cortical activity across the networks is greater during *Inscapes* compared to fixation cross. Across all three groups, the visual (theta, alpha, low and high gamma), default mode (alpha and low gamma), dorsal attention (alpha, beta, low and high gamma), ventral attention (alpha and low gamma), language (alpha and low gamma) and salience (alpha and low gamma) networks were significantly different between viewing conditions. Main effects of age on PSD are presented in Supplemental Fig. 2A.

Main effects of viewing condition on network connectivity strength were significant across all three groups in alpha and beta for wPLI (Fig. 2B), and theta, beta, and low and high gamma for AEC (Fig. 2C). In all cases, connectivity was higher during the fixation cross resting-state compared to *Inscapes*. For alpha band wPLI connectivity, significant differences between fixation cross and *Inscapes* were found in all networks except the language network, while in beta, only the visual network was significant. For AEC, the main effects of viewing condition were found

**Table 1**  
Descriptive statistics for the clinical behavioural measures for the ADHD, ASD and TD children, along with corresponding statistical results from one-way ANOVAs comparing the three groups.

		ADHD	ASD	TD
IQ	Mean ± SD	106.27 ± 9.92	99.59 ± 15.78	110.36 ± 10.45
	F-statistic	6.34		
	p-value	$2.55 \times 10^{-3}$		
	Post-hocs:	ADHD-ASD: 0.06; ADHD-TD: 0.40; *ASD-TD: $2.28 \times 10^{-3}$		
CBCL-AP	Mean ± SD	93.45 ± 7.19	87.67 ± 13.14	55.13 ± 7.01
	F-statistic	140.58		
	p-value	$4.98 \times 10^{-31}$		
	Post-hocs:	*ADHD-ASD: 0.03; *ADHD-TD: $9.56 \times 10^{-10}$ ; *ASD-TD: $9.59 \times 10^{-10}$		
SCQ-TOT	Mean ± SD	6.10 ± 5.41	18.48 ± 6.42	2.36 ± 2.40
	F-statistic	95.77		
	p-value	$1.19 \times 10^{-24}$		
	Post-hocs:	*ADHD-ASD: $9.56 \times 10^{-10}$ ; *ADHD-TD: 0.01; *ASD-TD: $9.56 \times 10^{-10}$		
ABAS-GAC	Mean ± SD	84.21 ± 14.64	67.50 ± 13.26	100.32 ± 15.38
	F-statistic	46.05		
	p-value	$5.17 \times 10^{-15}$		
	Post-hocs:	*ADHD-ASD: $4.22 \times 10^{-6}$ ; *ADHD-TD: $7.21 \times 10^{-5}$ ; *ASD-TD: $9.56 \times 10^{-10}$		

ADHD: attention-deficit/hyperactivity disorder; ASD: autism spectrum disorder; TD: typical developing; IQ: Intelligent quotient; CBCL-AP: The Child behaviour Checklist attention-problems subscale; SCQ-TOT: Social Communications Questionnaire total score; ABAS-GAC: Adaptive Behaviour Assessment System-II General Adaptive Composite; SD: standard deviation.



**Fig. 1.** . Group means and standard deviations for the number of epochs and head motion for the ADHD (blue), ASD (orange) and TD (yellow) participants for the fixation cross resting-state (solid) and *Inscapes* (hatched) pre- and post-epoch matching. Note that since after matching, the number of epochs was the same for both viewing conditions, the data are presented across the two conditions.

in the attention and visual networks in the theta frequency band, while only the visual network was significant in beta. Finally, in both gamma bands, AEC connectivity strength was significantly different between viewing conditions in the salience network, while the ventral attention and default modes were also significant in low gamma. Main effects of age on wPLI and AEC connectivity are presented in Supplemental Figs. 2B and 2C, respectively.

Interestingly, when comparing all three diagnostic groups, there were no significant main effects of group nor group-by-viewing condi-

tion interactions in any frequency band on PSD, wPLI network connectivity strength, or AEC network connectivity strength. Thus, exploratory pairwise analyses were performed to further investigate the main effect of group and group-by-viewing condition interactions beyond the omnibus test. As pairwise tests are more focused and have increased power to identify differences than an overall omnibus test, it is recommended that pairwise tests be carried out regardless of significance of the omnibus test (Hsu, 1996). When examining just the TD and ASD participants, a significant effect of group was observed in high gamma: the ASD participants showed significantly greater gamma power ( $F(1, 75)=7.92$ ,  $p_{corr}=0.0437$ ) compared to the TD in the visual network (Fig. 3). No significant differences in PSD, wPLI connectivity or AEC connectivity were observed between the TD and ADHD nor ASD and ADHD participants.

Only one group-by-viewing condition interaction was found in wPLI connectivity in high gamma within the salience network when comparing ASD and ADHD participants ( $F(1,85)=10.54$ ,  $p_{corr}=0.0468$ ). Post-hoc tests revealed that the ASD participants had significantly higher connectivity during the fixation cross resting-state than both the *Inscapes* and the fixation cross resting-state in the ADHD participants (Fig. 4).

#### 4. Discussion

*Inscapes* was designed to minimise participant head motion through engagement while suppressing the complex task-induced responses produced by narrative-driven, social movies (Vanderwal et al., 2015). Pre-matching, within our typically developing cohort of children, there were significantly more useable epochs in the *Inscapes* compared to the fixation cross resting-state, and of these usable epochs, *Inscapes* significantly reduced head motion compared to a fixation cross resting-state. These effects were also found across the combined ADHD, ASD and TD participants. Thus, if *Inscapes* is used in place of a fixation cross resting-state, not only are more epochs available for analyses with an identical scan time, but the remaining epochs are cleaner. Larger numbers of clean data epochs increases statistical power and thus the potential to identify significant effects (Boudewyn et al., 2018), without coming at the expense of longer scan times, a particular advantage when studying children and clinical populations. Also, the ASD participants had significantly fewer epochs remaining compared to the TD participants only in the fixation cross resting-state, suggesting that *Inscapes* may normalize head motion in clinical populations known to move more in the scanner (Yerys et al.,

Significant effects of viewing condition across the ADHD, ASD, and TD participant:

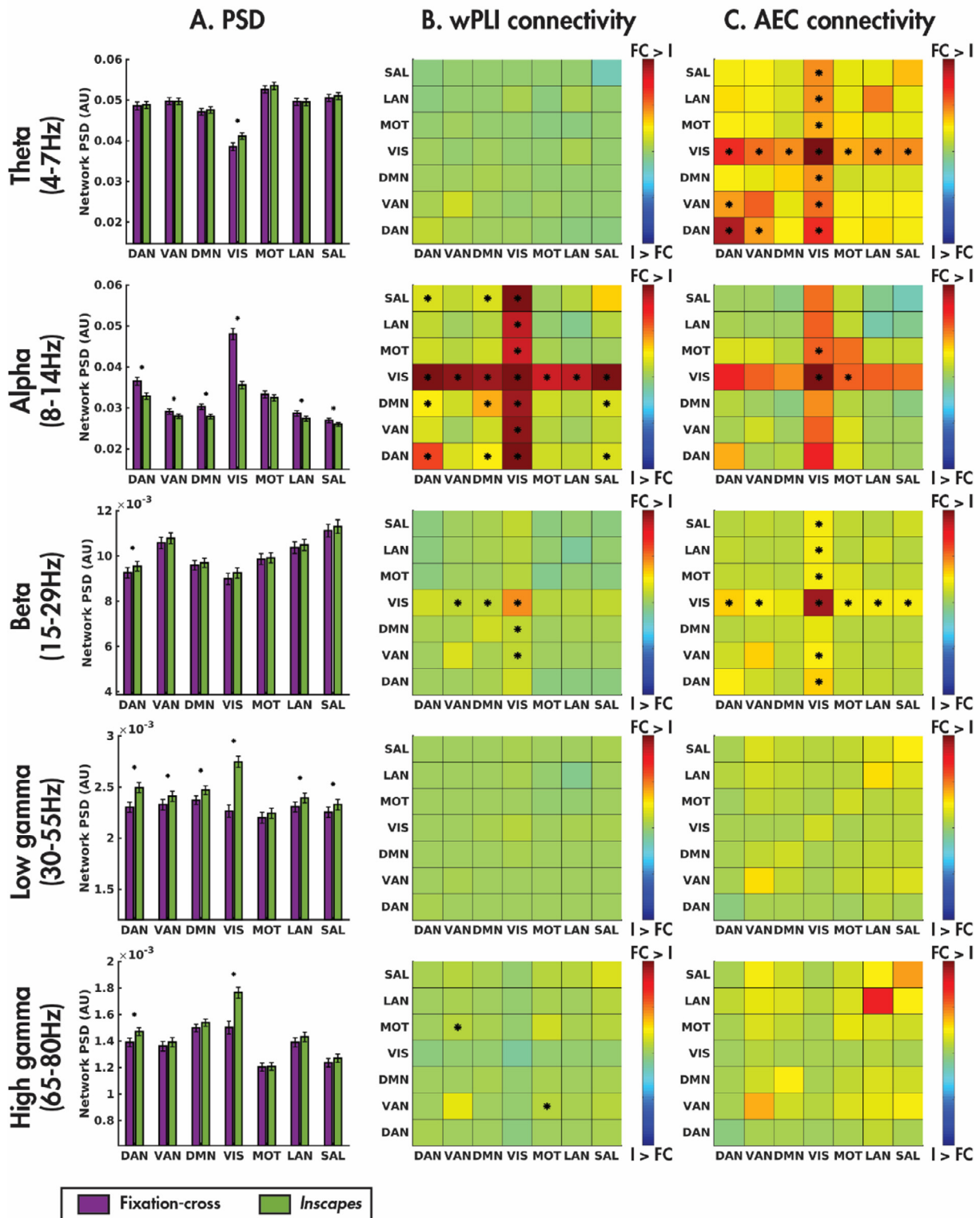


Fig. 2. . Main effects of viewing condition. Across the ADHD, ASD and TD participants, mean PSD (A), with standard error, in the fixation cross resting-state (purple) and *Inscapes* (green) across the seven resting-state networks (DAN: dorsal attention network, VAN: ventral attention network, DMN: default mode network, VIS: visual network, MOT: motor network, LAN: language network, SAL: salience network) and differences in mean within- and between-network wPLI (B) and AEC (C) connectivity are presented. Data are presented for each of the five frequency bands (theta: 4–7 Hz, alpha: 8–14 Hz, beta: 15–29 Hz, low gamma: 30–55 Hz, and high gamma: 65–80 Hz), and significant main effects of viewing condition ( $p_{corr} < 0.05$ ) are indicated by an asterisk.

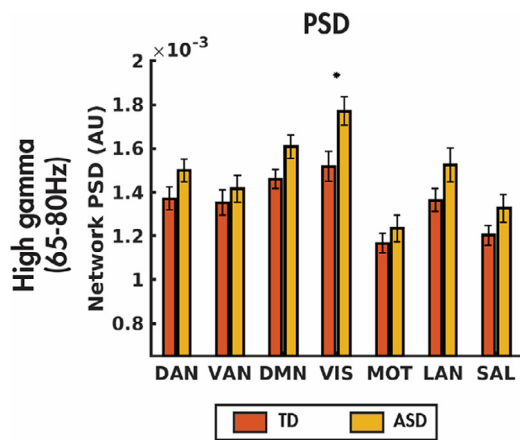


Fig. 3. Means and standard deviations across viewing conditions of the TD (red) and ASD (yellow) participants for PSD in high gamma (65–80 Hz). Data are presented for each of the seven resting-state networks (DAN: dorsal attention network, VAN: ventral attention network, DMN: default mode network, VIS: visual network, MOT: motor network, LAN: language network, SAL: salience network); only the VIS network showed a significant main effect of group ( $p_{\text{corr}} < 0.05$ ).

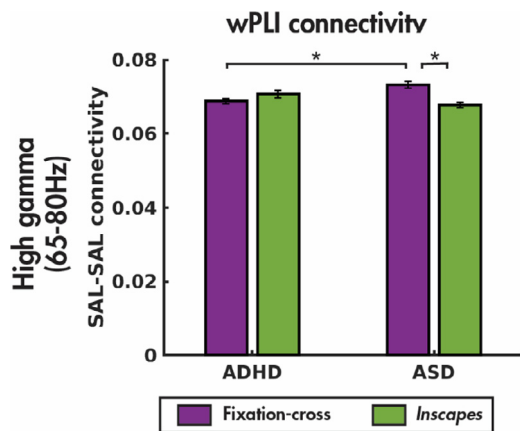


Fig. 4. Means and standard deviations for the fixation cross resting-state (purple) and *Inscapes* (green) in the ADHD and ASD participants for wPLI connectivity within the salience network in high gamma (65–80 Hz), with a significant difference between viewing conditions in the ASD participants indicated by an asterisk ( $p_{\text{corr}} < 0.05$ ) and between groups for the fixation cross resting-state.

2009). Combined, our results bolster *Inscapes* as an advantageous alternative technique to resting-state to study children and clinical populations, extending this from fMRI to MEG studies.

Elevated local cortical activity was found during *Inscapes* compared to a fixation cross resting-state, and the most pervasive effects were found in alpha and low gamma where all but the motor network were implicated. Although similar patterns were observed in high gamma, only the dorsal attention and visual networks reached significance. Decreases in alpha band power have been shown to be related to visual attention (Rajagovindan and Ding, 2011), while increases are thought to be a mechanism for suppressing distracting information (Foxe and Snyder, 2011). The widespread alpha band power decreases during *Inscapes* compared to fixation cross reflect a reduction of the inhibitory effects of alpha to support the increased neural demands required to process the inherently more complex movie, and are consistent with findings using EEG (Espenhahn et al., 2020). Local gamma activity across the brain has been reported to be higher during wakefulness than sleep (Cantero et al., 2004), and higher during cognitive tasks compared to resting-state (Fitzgibbon et al., 2004). Thus, similarly to alpha, we conclude that the widespread gamma power increases during *Inscapes* re-

fect a global increase in neural activity driven by the increased complexity and thus processing demands of *Inscapes* compared to a fixation cross, as observed in other task states.

Beta band power effects were localized to the dorsal attention network, while only the visual network showed increased cortical activity during *Inscapes* in theta. Enhanced beta activity has classically been associated with increased vigilance (Belyavin and Wright, 1987; Sherman et al., 2016; Townsend and Johnson, 1979), suggesting that the increased beta power in the dorsal attention network, a network responsible for maintaining the attentional focus (Corbetta et al., 2008), reflects enhanced vigilance during the presentation of *Inscapes* compared to a fixation cross. Attention to motion is known to modulate activity in visual cortex (Somers et al., 1999; Watanabe et al., 1998), and activity in the theta band has been shown to be indicative of synchronization between task-relevant brain regions (Mizuhara and Yamaguchi, 2007; Molinaro et al., 2013; Solomon et al., 2017). Thus, *Inscapes* induces increased, local activity in the visual cortex in the theta band to potentially enable task-specific long-range connectivity.

Increases in local activity during *Inscapes*, however, were accompanied by increased segregation/decoupling of the visual network, similar to findings in adults by Betti and colleagues. They reported decreased connectivity within and between intrinsic resting-state networks to movies in the alpha band (Betti et al., 2013) and in the beta band to time-scrambled movies (Betti et al., 2018), hypothesizing that these effects were being driven by a suppression of the idling intrinsic networks to support task processing. When examining the pairwise network connectivity strength in alpha and beta, along with theta, connectivity strength within and between the visual network was significantly decreased in *Inscapes*. Thus, enhanced local activity, indicating the specialization of brain regions during the visual stimulation of *Inscapes*, is accompanied by a suppression of spontaneous cortical noise.

As hypothesized, across frequency bands and MEG measures, the dorsal attention and visual networks were more frequently affected by the type of viewing condition, reflecting the increased visual and attentional load required by *Inscapes*. This coincides with findings of pronounced alterations in connectivity between these two networks in young children when watching traditional movies compared to resting-state (Emerson et al., 2015). The increases in the ventral attention network, responsible for the involuntary reorientation of attention to salient stimuli (Corbetta et al., 2008), suggest that throughout *Inscapes*, participants let their attention drift only to reorient to the slowly changing stimuli. Although still present, effects in the default mode network were less widespread, indicating that the task-negative network is still intact during *Inscapes*. In the seminal paper, Vanderwal et al. (2015) reported that mean connectivity within the default mode network did not differ between *Inscapes* and resting-state; however, connectivity was measured using fMRI with a temporal resolution of 2.5 s. In contrast, we took advantage of the far superior temporal resolution of MEG, and derived measures of local cortical activity and long range connectivity from ten second long timeseries with a sampling rate of 600 Hz. Although our connectivity findings coincide with no within-DMN differences between the two viewing conditions, we observed local cortical activity increases during *Inscapes* compared to resting-state which were localized to the alpha and low gamma frequency bands. Thus, we believe that the increased temporal resolution offered by MEG was able to identify frequency-dependant changes in local cortical activity that would not have been observable using fMRI.

Importantly, no group-by-viewing condition interactions were found in the omnibus analyses. Although the current study demonstrates that using *Inscapes* in place of fixation cross methods has significant effects on MEG measures across typical and atypical children (and others have demonstrated similar effects in TD children and adults using fMRI (Vanderwal et al., 2017, 2015)), we are the first to demonstrate that these observed differences are largely stable in clinical populations known to demonstrate sensory abnormalities, such as ADHD and ASD. The fact that we found no evidence of viewing condition interactions

between TD and clinical populations is important, allowing studies using *Inscapes* to be interpreted appropriately with respect to the existing body of literature using a fixation cross resting-states. However, it should be noted that in healthy adults, an unsupervised identification algorithm correctly identified individuals from data acquired while watching a traditional movie (specifically, *Oceans Eleven*) 100% of the time, outperforming both *Inscapes* (97%) and resting-state (90%). In clinical populations with a high degree of heterogeneity in neurobiology, such as NDDs (Anagnostou and Taylor, 2011; Ellegood et al., 2015; Kushki et al., 2019), individual variations may be of greater importance than when studying typically developing populations, and thus although *Inscapes* outperformed a fixation cross resting-state in identifying individual differences, traditional movies might be more advantageous. Future work investigating the ability to identify individuals with NDDs from movies, *Inscapes* and resting-state would help to address this issue.

Although there were no significant main effects of group in PSD or connectivity across the ADHD, ASD and TD participants, exploratory pairwise analyses revealed a difference between the TD and ASD participants in the visual network in high gamma. Furthermore, a significant interaction was found in high gamma wPLI connectivity in the salience network. The pairwise tests are more focused and have increased power to identify differences than the overall omnibus test; thus, we followed the recommendation that pairwise tests are completed regardless of the results of the omnibus test (Hsu, 1996). Gamma oscillations are generated by microcircuits of neuronal ensembles, consisting of interconnected gamma aminobutyric acid (GABA) inhibitory interneurons and pyramidal cells (Bartos et al., 2007), and the properties of the oscillations are dependant on the balance between cortical excitation and inhibition (Brunel and Wang, 2003). Furthermore, individual variability in peak gamma frequency is positively correlated with visual cortex GABA concentration (Muthukumaraswamy et al., 2009). The aetiology of ASD has been argued to be an excitatory-inhibitory imbalance in neural systems (Cornew et al., 2012; Rubenstein and Merzenich, 2003; Tebartz Van Elst et al., 2014) caused by an increase in excitatory glutamate neurotransmitters and a decrease in inhibitory GABAergic neurotransmitters (Rojas et al., 2015). Thus, it is not surprising that atypical gamma was found in ASD, and our results of atypical gamma power in ASD align with a variety of studies (see (Dickinson et al., 2016) for a review). Sensory hyper- and hypo-sensitivities, including visual dysrhythmia, are often reported behaviourally in ASD along with perceptual dysregulation (Baum et al., 2015; Leekam et al., 2007; Simmons et al., 2009), supporting our finding of altered gamma activity in the visual network in ASD compared to TD, particularly since oscillations in the gamma band are also linked to sensory processing, including visual processing (Fries, 2009). The salience network which is involved in switching between internally focused networks, such as the DMN, to externally focused networks, such as executive networks (Menon and Uddin, 2010), has been implicated in the over-sensitivity to sensory information in ASD (Green et al., 2016). There have been previous fMRI reports of hyperconnectivity of this network at rest in children and adolescents with ASD (Uddin et al., 2013). Our results demonstrated that the heightened connectivity of this network is specific to a fixation cross resting-state and is moderated by *Inscapes*.

There are several limitations to this study. First, our participants are spread over a wide age range; although the diagnostic groups did not differ by age, it is possible that given a larger sample, interactions with age would emerge. Second, to better understand how *Inscapes* affects the ability to identify individuals from neuroimaging data, and to help contextualize and assess the *Inscapes* versus resting-state comparison, future studies should examine a full comparison between other task conditions, such as traditional movies, along with *Inscapes* and a fixation cross resting-state. Combining our findings with those from other studies (Vanderwal et al., 2019, 2017, 2015; Wang et al., 2017), we hypothesize that extending our results to the three conditions would form a continuum, with fixation cross resting-state on one end, traditional movies on the other, and *Inscapes* in between, occupying a space

closer to resting-state as it was designed. The findings in the current study, particularly with respect to connectivity, are limited to lower frequency bands and driven by alterations within and between visual regions. Thus, these observed moderations of the idling intrinsic networks would be heightened by a traditional movie, and extend into the higher frequency bands responsible for the higher-order cognitive processing demands required by complex social movies. However, we note that finding a movie equally suitable for clinical populations and wide age ranges is difficult. Finally, due to the exploratory nature of our pairwise analyses, *p*-values were only corrected for the number of examined networks for PSD and the number of unique network pairs for connectivity, and not the number of pairwise comparisons performed; results should be interpreted accordingly.

In summary, we found that across typically developing and clinical children and adolescent populations, *Inscapes* reduces head motion and yields cleaner MEG signal compared to a fixation cross resting-state. However, *Inscapes* increases local activity indexed by oscillatory power across all canonical frequency bands. The increases in local activity is concomitant to decreases in neural synchrony and coupling in slower frequencies between resting-state networks, primarily the visual network, reflecting a release from inhibition which dominates in the spontaneous intrinsic networks during resting-state. Importantly, these differential effects are stable across TD participants and those with ADHD and ASD. Thus, *Inscapes* is well-suited to investigate resting brain function in young and/or clinical populations who are difficult to scan, provided the data are interpreted appropriately in light of the more extensive fixation cross literature and task literature when affected networks and bands are being investigated.

#### Data availability statement

Raw data used in the current study are currently in the process of being made available via a public repository, Brain-CODE (Vaccarino et al., 2018).

#### Declaration of Competing Interest

E. Anagnostou has served as a consultant to Roche and Quadrant Therapeutics, holds a patent for the device, "Anxiety meter", and has received in kind support from AMO pharma, royalties from APPI and Springer, and editorial honoraria from Wiley. The remaining authors (M. M. Vandewouw, B. T. Dunkley, J. P. Lerch, and M. J. Taylor) have reported no biomedical financial interests or potential conflicts of interest.

#### Credit authorship contribution statement

**Marlee M. Vandewouw:** Conceptualization, Methodology, Software, Formal analysis, Writing - original draft, Writing - review & editing, Visualization. **Benjamin T. Dunkley:** Methodology, Writing - review & editing. **Jason P. Lerch:** Writing - review & editing, Project administration, Funding acquisition. **Evdokia Anagnostou:** Writing - review & editing, Supervision, Project administration, Funding acquisition. **Margot J. Taylor:** Conceptualization, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.neuroimage.2020.117524](https://doi.org/10.1016/j.neuroimage.2020.117524).

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