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Measuring engagement of the executive control network from 3 months of age

Michelle Tran, *The University of Western Ontario*

Supervisor: Dr. Rhodri Cusack, *The University of Western Ontario*
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Abstract

The executive control network (ECN) is critical for higher cognition and executive function (EF). Despite its importance, no scientific consensus has been reached on how and when it begins to function. In the present study, we assessed the development of the ECN in awake infants less than a year old by employing functional magnetic resonance imaging (fMRI) and naturalistic stimuli. First, we identified evocative movies that engaged infant attention. We then transferred them into adult imaging to test for which movie evoked the highest ECN response. Strong ECN responses were evoked while viewing *Despicable Me*, therefore we implemented this movie into infant imaging. We found that as early as 3-months of age, infants showed a similar response to that of adults. Overall, we demonstrated a technique that could potentially gauge EF in very young infants and developed a tool capable of imaging awake infants under natural conditions.

Keywords: Executive control network, executive function, functional magnetic resonance imaging, infants, intersubject correlation, naturalistic stimuli

Co-Authorship Statement

Research presented was a collaborative effort. Under the supervision of Dr. Rhodri Cusack, he provided guidance and feedback on all aspects of Chapters 2 and 3. I aided in the design and analysis, collected all data, and wrote majority of both manuscripts. Laura Cabral assisted in coding and designing the paradigms in Chapter 2, which Dr. Cusack and I modified. Ronak Patel, an honor's thesis student of who I co-supervised with Dr. Cusack, annotated the movies for production elements in Chapter 2. Recently, Chapter 2 has been submitted for publication while Chapter 3 is in preparation for publication.

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Chapter 1: Introduction

Executive Control Network and Executive Function

The ability to voluntarily guide one's thoughts and actions is a crucial life skill. Commonly referred to as executive function (EF), it involves a series of high-level processes relating to impulse control, decision-making, working memory, cognitive flexibility, error detection, and conflict resolution (Diamond, 2013; Niendam, Laird, & Ray, 2012; Luna,Padmanabhan, & O'Hearn, 2010; Anderson, 2002; Duncan, 2001). Neurally, EF is strongly associated with a set of brain regions called the executive control network (ECN). Consisting of the dorsolateral prefrontal cortex (dlPFC), inferior parietal lobule (IPL), anterior cingulate cortex (ACC), and anterior insula cortex (AIC) (Gao & Lin, 2012; Niendam et al., 2012; Cole & Schneider, 2007; Duncan & Owen, 2000), numerous studies have reported that lesions to these neural substrates in adults (Owen, Downes, Sahakian, Pokey, & Robbin, 1990; Milner, 1982;) and primates (Diamond & Goldman-Rakic, 1989; Goldman-Rakic, 1987; Jacobsen, 1936), and in particular the dlPFC, produce impairments in EF. Although this bridge between the ECN and EF in adulthood has been a long field of active research, comparatively little is known about the ECN's early development and when it becomes functionally relevant.

Speculation on the onset of function in the ECN in human infants has stemmed from behavioral reports on the A*B* task and the delayed reaching (DR) task, both of which are intended to measure inhibitory control and working memory domains of EF. The A*B* task, originally created by Piaget (1954) to measure the concept of object permanence in children, involves an infant choosing which of two possible locations (A or B) contains a veiled object. While the infant watches, the object is hidden in location

A. Following a delay, the infant is given the opportunity to unveil the object. This scenario is then repeated until the infant has habituated to reaching towards location A. Once this has been established, while the infant watches, the object is hidden at location B. After a delay, the infant again searches for the object. On this occasion, the infant must inhibit the prepotent response to reach to the previously habituated position (location A) in order to answer the trial correctly. When this does not occur, the infant searches for the object in location A, producing an A*B* error. The DR task is similar to the A*B* task, except that in the DR task, the object is hidden at random. Therefore, while working memory is still required, there is less need for inhibitory control.

Early work showed that the dlPFC is needed for these tasks. Diamond and Goldman-Rakic (1989) demonstrated that monkeys with prefrontal lesions are incapable of performing the A*B* and DR tasks. However, monkeys who had an intact dlPFC retained correct reaching behavior. This suggested that inhibition to prepotent tendencies and memory processes were dependent on prefrontal function, and by extension that young infants that cannot perform these tasks do not have a mature prefrontal cortex. Interestingly, A*B* and DR performance increased with age, with extended delays required to evoke an error. From 7.5- to 12-months of age, infants were able to withstand 2-seconds longer each month, with 12-month old infants finding the hidden object correctly at both locations with delays as long as 10-seconds (Diamond & Doar, 1989; Diamond & Goldman-Rakic, 1989; Diamond, 1985). The progression in infant performance indicated that EF skill development followed a gradual trajectory that potentially coincided with neurophysiological developments in the dlPFC (Anderson, 2002; Diamond, 2002; Diamond & Goldman-Rakic, 1989).

However, is correct reaching behavior indicative of the earliest age of a functioning ECN? Diamond and colleagues (1989a,b,c ;1985) noted that infants under 7.5-months could not be tested on either the A*B* or DR task because of their inability to unveil the hidden object. This may be due to the task involving highly controlled motor responses that can only be seen in older infants. In addition, cognitive capacities related (i.e. task understanding) and unrelated to EF (i.e. visuomotor control and proprioception) that are required to carry out these tasks may not have surfaced yet. Hence inferences regarding a functioning ECN in younger infants was likely not plausible because correct reaching behavior was never instantiated or could not be measured. It has been argued therefore that a functioning ECN might be present earlier than previously reported (Cusack, Ball, Smyser, & Dehaene-Lambertz, 2016). One piece of evidence in support of this is that resting-state neuroimaging studies have identified the presence of an ECN at term birth (Doria et al., 2010). If this network is present, it could be functioning. However, this is difficult to confirm at present, as its corresponding behavior has not yet emerged in any way that can be reliably measured. Alternatively, young infants may exhibit EF but be allocating such energies towards operations that seem automatic in adults. More specifically, EF assignment may depend upon the cognitive demands triggered by an unfamiliar environment. For example, when adults participate in dual task paradigms, they demonstrate impaired EF on the second task because executive resources are being used on performing the first task. In line with this concept, infants are only beginning to construct schemas to understand their novel world saturated in distractions or dual tasks. As a result, environmental demands may be more accentuated in infants than in adults, leaving little EF reserves to carry out external tasks properly. Therefore, young infants may have EF, however require more before it can be explicitly present, quantifiable and operationalized (Cusack et al., 2016). The goal of this thesis is to probe for the presence of EF using a novel neuroimaging methodology.

Awake Infant Functional Imaging

Few studies have employed functional magnetic resonance imaging (fMRI) in awake infants because of the difficulty of minimizing the amount of motion they exhibit in the scanner. Although measures are taken to ensure the comfort of infants and to discourage movement, such as utilizing vacuum pillows, foam cushions and swaddles, even slight movement deviations can greatly impact the usability of the data. Up until now, researchers have primarily focused on assessing infants in either an asleep or sedated state as a means to limit movement. As a result, these studies are often restricted to using methods that examine whether networks are present, rather than the underlying functions subserved by the networks, as no stimuli or task is involved. Thus to robustly gauge and interpret ECN functionality, it seems pivotal that methods for richer stimulation be brought into the research design.

However to do this, is it necessary that infants must be awake? This probably depends on whether the systems of interest operate automatically or not. Different states of wakefulness have been shown to influence the neural signatures of the frontal cortex during task-based fMRI experiments (Portas et al., 2000; Drummond et al., 1999). In adults, reductions in functional connectivity of the ECN have been observed during anesthesia (Boveroux et al., 2010) and deep sleep (Heine et al., 2012; Sämann et al., 2011). These findings suggest that in order to measure reliable ECN responses indicative of natural cognitive processing, individuals must be consciously present.

Taken together, eliciting EF in infants necessitates them to be processing an engaging complex stimulus while awake. Successful execution of such a study must consider ways to reduce head movement in the scanner, such as using stimuli that are engaging enough to keep the infants awake and calm. In the following section, I describe a unique paradigm that addresses these concerns.

Naturalistic Audiovisual Neuroimaging

Naturalistic neuroimaging offers the opportunity to record neural responses during unconstrained movie viewing. Through intersubject correlation (ISC), a technique commonly applied to naturalistic fMRI data, we can quantify how similar or synchronized a group of individuals brain responses are to one another. Despite the unconstrained task and the complexity of the stimuli, well-directed movies show highly reliable, time-locked and functionally selective responses in many brain areas such as visual and auditory cortex, the ECN and other regions associated with higher cognition (i.e. default mode and dorsal attention network) (Vanderwal, Kelly, Eilbott, Mayes, & Castellanos, 2015; Naci, Cusack, Anello, & Owen, 2014; Hasson, Malach, & Heeger, 2010; Jääkeläinen et al., 2008; Hasson, Nir, Levy, Fuhrmann, & Malach, 2004).

Naturalistic viewing paradigms have been used to study developmental changes in brain function by comparing the neural time-series of 4- to11-year old children to that of adults. Recently, Cantlon and Li (2013) demonstrated that during the viewing of a *Sesame Street* video containing numerical and verbal content, children and adults showed high within-group ISC corresponding to sensory cortices and content-specific areas such as the intraparietal sulcus, known to be associated with numerical processing, and Broca's area, known to support language processes. To measure the degree of maturity in these corresponding regions, the within-group ISC of children was compared to the ISC between children-to-adults. Higher ISC within other children than with adults was found, suggesting that cognitive responses similar in adults were still maturing in children. Therefore by using a naturalistic paradigm and the time-course of adults as a benchmark, maturational changes in brain function could be inferred in pediatric populations.

Employing such a paradigm offers multiple advantages for awake infant imaging. First, no explicit task is involved. This removes the bottleneck of communicating the task instructions, which has proven to be a confound in other areas of infant assessment (Wellman, Cross, & Watson, 2001). In addition, unlike behavioral tasks, no explicit response is required, as fMRI quantifies cognitive processes in neural networks. Together, this gives the promise that these paradigms can be applied to any age group, and have the potential to be a powerful new tool to probe cognitive function. Second, imaging studies of children have suggested that by employing dynamic and engaging stimuli such as movies, attention can be sustained and motion limited, leading to more robust scanning in comparison to traditional fMRI paradigms in which static images were presented (Vanderwal et al., 2015; Cantlon & Li, 2013). As motion reduction has been a long-standing barrier to conducting fMRI studies in awake infants, naturalistic paradigms seem promising in circumventing this problem. Lastly, movies evoke strong and reliable, time-locked neural responses which can be analyzed via ISC. This will enable us to examine how the ECN develops in infancy and further allow us to infer maturity through conducting cross sample comparisons between infants and adults.

While it is challenging and uncommon to scan awake infants, it is achievable. In the past, three studies have examined infants during either visual (Biagi, Crespi, Tosetti, & Morrone, 2015) or auditory (Dehaene-Lambertz et al., 2009; Dehaene-Lambertz & Dehaene, & Hertz-Pannier, 2002) stimulation. These studies used block designs involving highly controlled, short-duration stimuli. Such methods enable the isolation of active brain regions to specific types of events, but cannot probe the types of complex processing that would take place naturally (Hassson, Furman, Clark ,Dudai, & Davachi, 2008). Therefore, in an effort to capture natural cognitive processing of the ECN across the first year in awake infants, we employed a movie-fMRI paradigm.

Rationale and Thesis Objectives

The prevailing view, based on behavioral research, is that EF comes online in the latter half of the first year, but in contrast to this, neuroimaging has indicated that it might be present at term birth. To investigate this, we have set out three research objectives to probe the maturation of the ECN in infants less than a year old.

1. Identify movies that engage infants. Using a looking time paradigm, we will quantify whether infants are sufficiently engaged by movies to remain still long enough for us to acquire neuroimaging data, and identify the movies that elicit the highest amount of visual attention.
2. Employ fMRI in adults to examine which movies evoke the ECN. Movies will first be presented to healthy adult individuals to find a stimulus that consistently

produces high ISC in the ECN. This will also characterize the adult response, which can be used as a reference against which infant responses can later be compared.

3. Scan awake infants using a naturalistic audiovisual paradigm. In doing so, we will be able to capture natural cognitive processing indicative of real-word mechanisms.

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Chapter 2: Easy Online Recruitment and Testing of Infants with Mechanical Turk

Introduction

Infants are difficult to recruit and test. Recruiting their busy caregivers requires broad advertising, collaboration with daycares or maternity hospitals, and labor-intensive relationship building. As a consequence, it often takes long periods of time to recruit a sufficient number of participants. Once recruited, the schedules of the caregiver, infant, research staff, and testing facilities must be coordinated, and practicalities such as transport resolved. Given these complexities, infant studies are relatively slow, expensive, and require patience and perseverance. This puts pressure on investigators to minimize the number of participants recruited and as result, studies are sometimes under-powered, reducing their reproducibility (Peterson, 2016), reflecting a broader issue in psychology (Open Science Collaboration, 2015). Thus to make it easier to conduct high quality infant research, it is imperative to find ways to reduce these pressures.

One solution may lie online. In recent years, the crowdsourcing engine, Amazon Mechanical Turk (MTurk) has become a central marketplace, bringing together hundreds of thousands of workers from over 100 countries to complete “Human Intelligence Tasks” (HITs) through a web browser for modest remuneration (Buhrmester, Kwang, & Gosling, 2011; Mason & Suri, 2011; Kittur, Chi, & Suh, 2008; Pontin, 2007). Often these tasks involve image annotation, rating surveys and demographic questionnaires using templates delivered by MTurk (Mason & Suri, 2011; Paolacci, Chandler, & Ipeirotis, 2010). However, by employing external websites, requestors can generate more complex tasks that meet the demands of their experimental needs (Goodman, Cryder & Cheema, 2013; Burhmester et al., 2011; Mason & Suri, 2011). In combination with MTurk's simple interface and flexibility, this lends itself well to the fast and cost effective collection of data.

Recently, experimental psychologists have used MTurk to obtain data from adults on simple tasks (Sweeny, Andrews, Nelson, & Robbins, 2015; Lewis, Sugarman, & Frank, 2014; Starmans & Bloom, 2012; Piff, Stancato, Côte, Mendoza-Denton, & Keltner, D., 2011). Parental report measures of child behavior have also been documented (Schneider, Yurovsky & Frank, 2015), however to our knowledge, direct testing of infants has never been attempted. Therefore, the aim of the present study was to examine whether MTurk could be used to recruit and test infant populations. To address this, we implemented a task that aimed to quantify looking time to a set of video stimuli in infants aged 5- to 8-months. Specifically, infants viewed children's television programs, and attention was quantified by measuring when infants fixated on the screen using their webcam.

Methods

Participants

Ethical approval was obtained from Western University's Health Sciences Research Ethics Board (see Appendix A). We recruited infants aged 5- to 8-months old using MTurk (Amazon, Seattle, Washington). All workers of MTurk remain de-identified, and are only referred to by a unique worker identity code provided by Amazon. To participate, infant caregivers provided informed consent, and were required to have a webcam, speakers and Adobe FLASH. The same experiment was administered in two independent batches, differing in compensation rate. During the first batch, 63 participants were recruited over the course of a week, reimbursing them at $1.25. To motivate increased participation, remuneration in the second batch was raised to $5.00, leading to 84 participants being recruited within the following six days. Altogether, 147 participants were recruited. However, due to the quality control requirements of our study and the difficulty of infant testing in general, 90 were excluded. Reasons included technical issues likely associated with internet connectivity (no webcam video being obtained from the server, the webcam video not being in sync with the movie), or aspects of testing configuration such as the infant's eyes not being visible in the webcam video. In addition, infants who did not have English as their primary language were also excluded. Of the 57 participants (*M* = 6.49 months, *SD* = 0.93) included in the study, 9 were 5-month old, 19 were 6-month old, 21 were 7-month old and 8 were 8-month old.

Stimuli and Video Recording

Ten movie clips between 9- and 13- minutes in length were used as stimuli. They were taken from popular programs designed to appeal to infants and children: *Baby Einstein*, *Blues Clues*, *Curious George*, *Despicable Me*, *Dora the Explorer*, *The Program with the Mouse*, *In the Night Garden*, *Teletubbies*, *Timmy Time* and *Up*. To present the movies and record from the webcam, FLASH was used (Adobe, San Jose, California). Content was provided from and recorded to a computer in the Amazon cloud (Amazon, Seattle, Washington) running Wowza Media Streaming Server (Wowza, Golden, Colorado) using real-time streaming protocols. Our software is available on request.

Procedure

The HIT was created and posted on MTurk under the title “Infant Television Viewing”. Participants viewed a webpage detailing compensation rate, the allotted time to complete the HIT, expiration date of the HIT, a short description of the task and the required qualifications. After accepting the HIT, participants were directed to a webpage that provided an information sheet and asked for their informed consent. Consent was obtained via online checkbox and button press. This was followed by an evaluation of the suitability of the participant’s computer, software, webcam, speakers, and internet connectivity. To do this, we recorded a brief 5-second video of the caregiver and their infant, and asked them to move and make sounds. This video was then played back to the caregivers, and they were asked to check a box to indicate whether or not they were able to see and hear themselves. If they indicated they could not, they were thanked and excluded from participation. Otherwise, they were directed to a new webpage instructing them to position their infant on their lap, in the center of the screen and in a well-lit room. This was specified to ensure that the infant’s eyes were visible while recording the webcam video. Once in a comfortable position, caregivers were instructed to press a ‘start’ button to commence the experiment. One of ten pseudo-randomly selected movies was then presented. Afterwards, participants completed a short demographic questionnaire from which the age and language background of the infant was obtained.

Video Annotation

The time-course of overt attention was measured from the recorded webcam videos. Using the free Anvil tool (Kipp, 2001), the experimenter and a second observer annotated when in the movie each infant fixated on the screen. The two observers agreed in their assessment of looking time 99.81% of the time with a corrected kappa of 0.41.

Are Some of the Movies More Engaging Overall?

We first quantified overall looking time, by calculating the proportion of attention in a movie for each infant. This proportion was then arcsine transformed to increase the normality of its distribution. To assess whether some movies were more engaging than others, we used a two-way ANCOVA with factors of movie (10 levels) and infant age (in months). Post-hoc *t*-tests were then used to compare pairs of movies.

Are Some Parts of the Movies More Engaging to Infants than Others?

To determine whether the looking times were consistent within a movie, we conducted a correlation analysis that assessed the time-course of attention. Our hypothesis was that if particular parts of a given movie were more engaging than others, greater similarity would be seen for the time-courses of attention from infants viewing the same movie than those viewing different movies. A 'binning' technique was applied in which each time-series was divided into 0.5 s intervals and assigned a 0 (not looking) or 1 (looking). Due to the movies having different run times, we restricted the analysis of the time-series data to the duration of the shortest movie (552.50 s or 1105 bins).

To quantify the similarity, the Pearson correlation between the time-course of each participant and each other participant was computed. A correlation of 1 would reflect identical time-courses, and a correlation of 0 would represent no correspondence. We tested the hypothesis that infants watching the same movie should have a more similar time-course than infants watching different movies. To do this, the mean of within-movie correlations was calculated. This was then tested against a null distribution calculated by bootstrapping, randomly shuffling the matrix of pairwise Pearson correlations of participants and taking the mean positions in the matrix that previously held within-movie comparisons. The process was repeated 100,000 times to build the null distribution. The proportion of null values that were greater than the true value was taken as the *p*-statistic.

What Features Make the Movies More Engaging?

We furthermore assessed what cinematic features of the movies were driving the infants' attention. To address this, we annotated the top five movies that showed the highest proportion of looking time for production elements prominently found in infant television programs (Goodrich, Pempek, & Calvert , 2009). Ten production features were annotated for and included faces, action (high and low), camera techniques (camera cut, zoom, scene change) and auditory (background music, singing and rhyming, sound effects, vocalizations) elements of the movie (Table 1). Linear regression was then used to test which cinematic features of a movie predicted the time-course of infant's fixation. The regression coefficient for each cinematic feature was tested against zero using a one-sample t-test across infants.

Table 1

Taxonomy and descriptions of the 10 production features. The table is a modified version of that created by Goodrich and colleagues (2009).

Feature	Description
Low action	Low levels of character and/or object movement onscreen
High action	Rapid character and/or object movement onscreen
Camera cut	Abrupt change from one camera shot to another within the same scene
Camera zoom	Camera continuously moves away or towards an object or character within a scene
Scene change	A shift from one scene to another
Background music	Music presented with dialogue and/or other sounds
Vocalization	On-screen non-language sound made by a character
Sound effect	Sounds other than dialogue or music which are edited into the auditory element of a given scene (i.e. drum rolls, a whistle, etc.)
Singing and rhyming	Presenting words melodically and/or in a rhyming scheme
Face	Visual presentation of facial features (eyes, nose, lips) holistically in the form of faces

Results

Are Some of the Movies More Engaging Overall?

Figure 1 and Table 2 show the proportion of attention by movie. There was a main effect of movie on attention time ($F(9, 25) = 3.56$, $p < .001$, $\eta^2 = 0.562$,) (Figure 1). Post Hoc comparisons using Tukey's Honestly Significant Difference (HSD) revealed that *Curious George* ($M = 0.33$, $SE = 0.09$) engaged infants significantly less than *In the*

Night Garden (*M* = 0.74, *SE* = 0.06, $p < .05$), *Teletubbies* (*M* = 0.70, *SE* = 0.09, $p < .05$) and *Timmy Time* (*M* = 0.68, *SE* = 0.04, $p < .05$). Age was not found to modulate looking time ($F(3, 25) = 2.74$, *ns*, $\eta^2 = 0.248$).

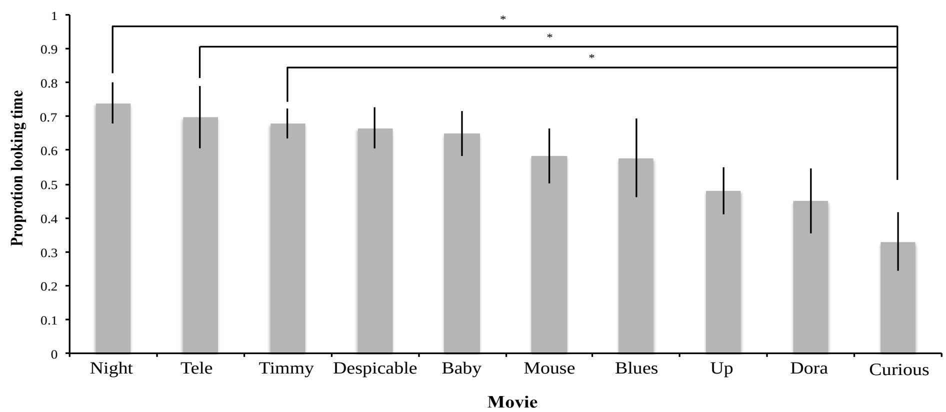

Figure 1. Mean proportion looking time across movies (*n* = 57). Error bars represent +/-1 standard error. Key to movies: Baby, *Baby Einstein*; Blues, *Blues Clues*; Curious, *Curious George*; Despicable, *Despicable Me*; Mouse, *The Program with the Mouse*; Night, *In the Night Garden;* Tele, *Teletubbies*; Timmy, *Timmy Time*; and Up, *Up*.

Table 2

Mean proportion looking times for each movie, collapsed across age.

	Movie									
	Baby	Blues	Curious	Despicable	Dora	Mouse	Night	Tele	Timmy	Up
Proportion looking time	0.65	0.58	0.33	0.66	0.45	0.58	0.74	0.70	0.68	0.48
SE	0.07	0.12	0.09	0.06	0.10	0.08	0.06	0.09	0.04	0.07
n	5	5	6	5	7	6	5	6	7	5
Run time (s)	604.94	652.02	767.02	680.64	654.02	637.03	735.36	552.92	580.00	736.01

Are Some Parts of the Movies More Engaging to Infants than Others?

Figure 2 shows the binned time-courses of attention for each of the infants, grouped by movie. By eye, there do appear to be some parts of some movies where infants start or stop paying attention together. However, not surprisingly there are also large individual differences, as infants may have varying stimulus preferences, or be spontaneously thinking of different things.

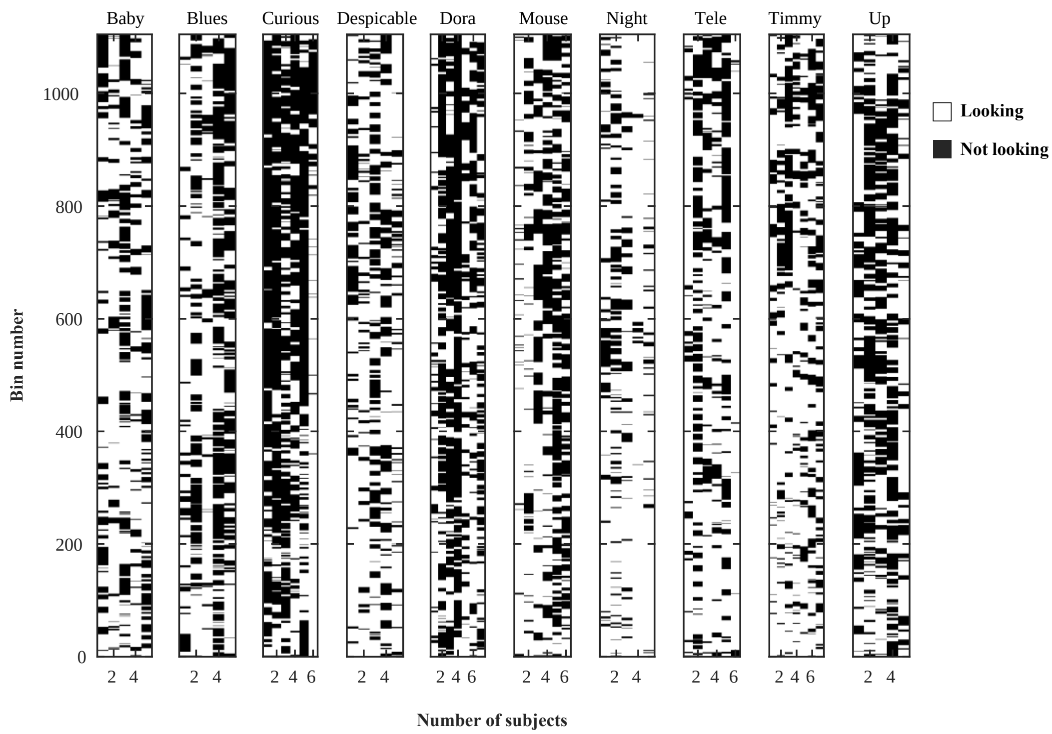

Figure 2. Binned time-courses of attention for infants grouped by movie.

We therefore evaluated statistically whether infant attention was modulated by the content of the movies. The correlation in the time-course of attention across participants watching the same movie was positive but weak ($r = 0.07$). However, this was highly significant, when compared to the null distribution calculated through bootstrapping (Figure 3, $p < .001$), confirming that the movie content modulated infant attention.

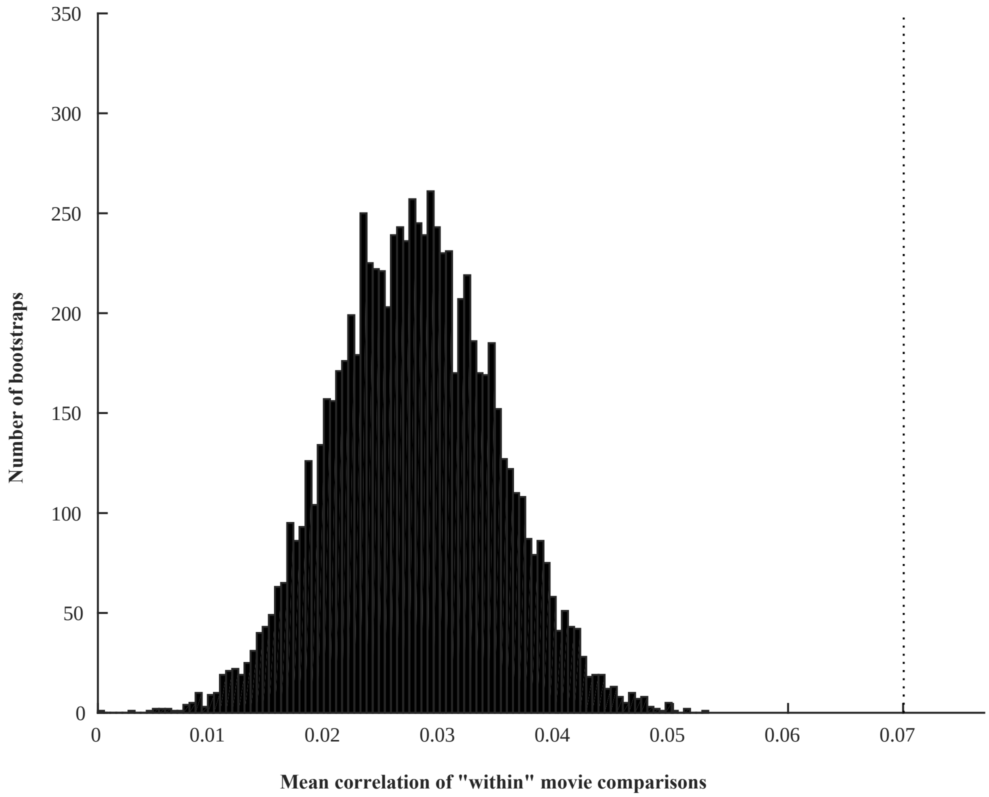

Figure 3. Null distribution created from shuffling the mean of within-movie correlations. Dotted line represents the true measured correlation of the time-course of attention across participants watching the same movie, which was well outside the null distribution.

What Features Make the Movies More Engaging?

For the five movies for which cinematic annotations were available (Figure 4), we used linear regression to investigate what drove infant attention. As no effect of age was seen in the overall looking time, we collapsed across ages and grouped infants by the movie they viewed ($n = 28$). From the 10 annotated features (Table 1), it was found that singing and rhyming ($t(27) = 2.60$, $p < .05$), camera zooms ($t(27) = 2.16$, $p < .05$) and faces ($t(27) = 2.98$, $p < .01$) significantly increased movie engagement (Figure 5).

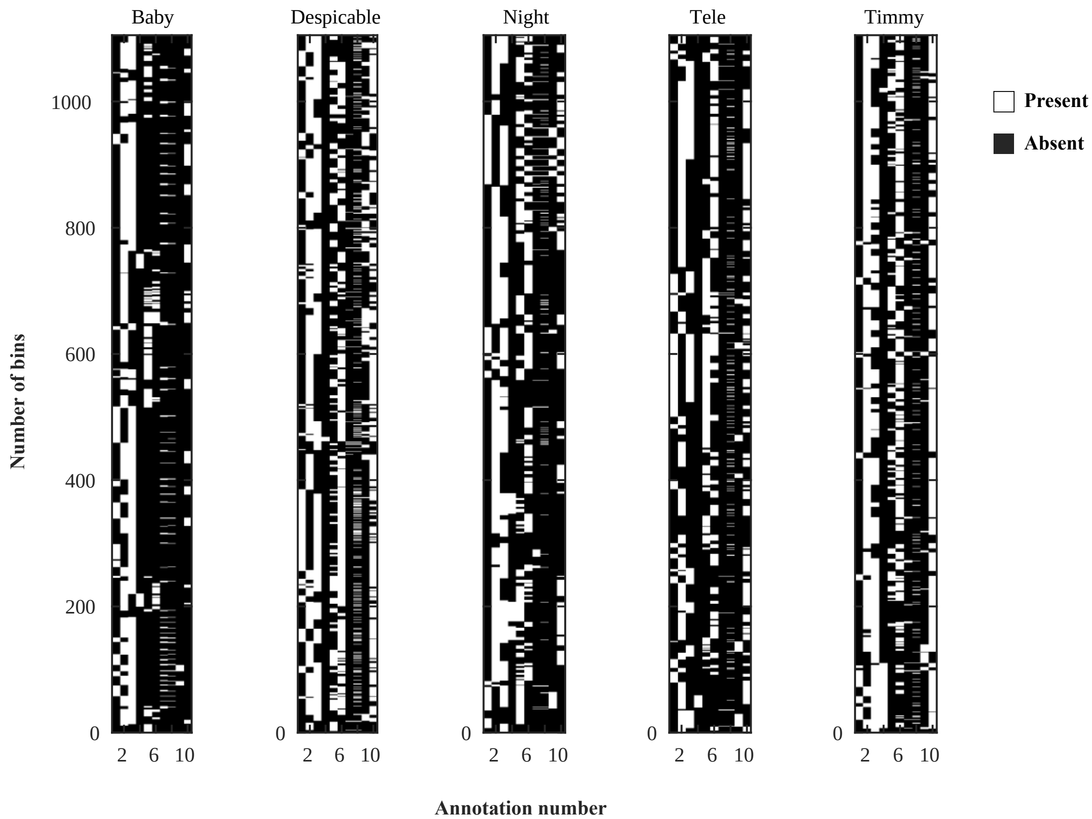

Figure 4. Binned time-courses of movies with annotated cinematic features. Annotated elements were respectively: 1) high action; 2) low action; 3) background sounds; 4) singing and rhyming; 5) sound effects; 6) vocalizations; 7) scene change; 8) camera cut; 9) camera zoom; and 10) presence of face.

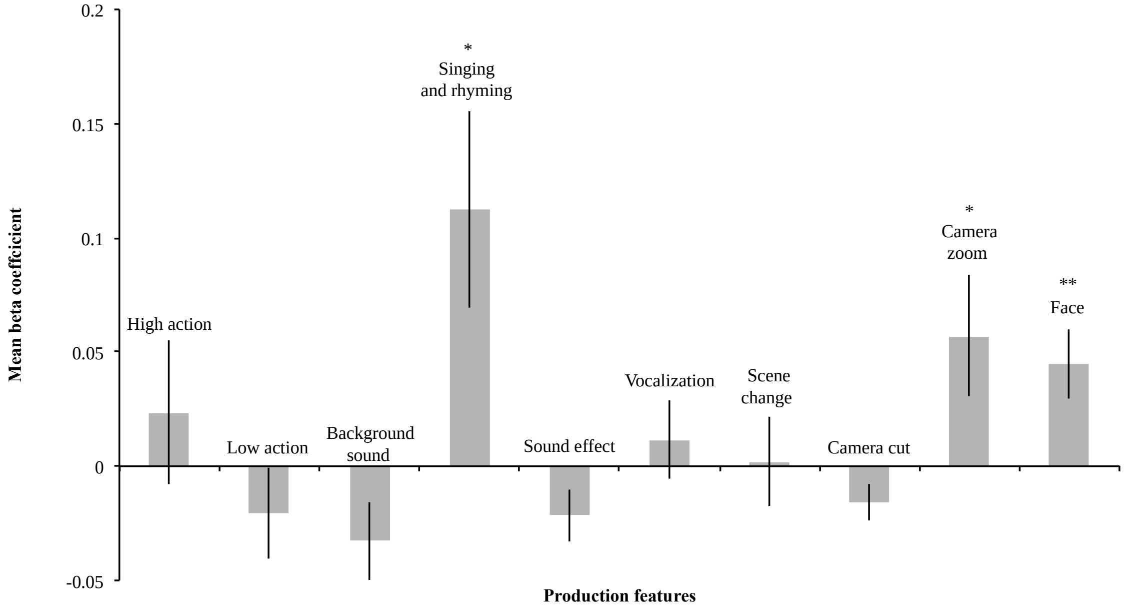

Figure 5. Mean beta coefficients for production features across movies (*n* = 28). Error bars represent +/-1 standard error.

Discussion

Our experiment proves the principle that MTurk can be used as an efficient tool to recruit infants. In a looking time paradigm, we showed that infants aged 5- to 8-months were engaged by different child-directed movies more so than others, that some parts of the movies were more engaging than others, and that the cinematic features of faces, singing and rhyming, and camera zooms within the movie increased attention. No age differences in attention were found. Most importantly, we report for the first time of an online experiment capable of capturing and quantifying infant behavior directly.

Our finding that infants demonstrate preference for faces and face-like stimuli even in the midst of distractors and dynamic visual scenes is supported by a substantial existing literature (Franchak, Heeger, Hasson, & Adolph, 2015; Di Giorgio, Turati, Althoè, & Simion, 2012; Frank, Vul, & Johnson, 2009; Farroni et al., 2005). Similarly, our finding that singing and rhyming attract attention concurs with previous reports indicating preferences for engaging melodies over dissonant sounds (Costa-Giomi & Ilari, 2014; Nakata & Trehub, 2004; Trainor, Tsang, & Cheung, 2002; Trainor, 1996). High engagement towards both of these cinematic elements has been associated with internal biases reflective of maternal behavior and infants' keen interest to attend to stimuli rich in social information (Nakata & Trehub, 2004; Bushnell, Sai & Mullin, 1989).

In addition, camera zooms also recruited increased visual attention. The effect of camera zooms has rarely been studied. An existing report found that preschool-aged children and toddlers demonstrated unchanged or reduced visual attention when camera zooms were present compared to when they were absent (Susman, 1978; Levin & Anderson, 1976). These authors suggested that camera zooms deter attention because of its tendency to disrupt the visual flow of content by taking the viewer from a whole to part perspective. The difference between these results and ours may be due to the different ages of the infants tested, or to the very different stimuli. For example, the camera zooms in our stimuli served an artistic or communicative vision determined by the movie directors, and thus may have been more congruent with the overall content in comparison to Susman's study.

MTurk recruitment was found to be easy, and enabled us to collect a large infant data set in a relatively short period. Unlike in the laboratory where local participants are tested one at a time, MTurk permits workers from across the world to carry out the same HIT in parallel (Mason & Suri, 2011; Paolacci et al., 2010). The service is entirely online which allows caregivers to recruit their child in the convenience of their own home without having to worry about the demands that a novel environment imposes on their child and restrictive participation time slots. Reflecting this increased convenience for participants, subject payments were much lower than in typical studies.

While recruitment was easy, there was a tradeoff in data quality. Due to our limited control in screening participants and their equipment online, many workers (approximately two thirds of our data) had to be excluded from our analyses. Although we implemented screening measures to constrain who could complete and view the HIT, majority of exclusions were due to issues regarding internet connectivity rather than task performance. Therefore although internet is inherently involved in using MTurk, in order to enhance data quality when bi-directional video streaming is required, internet speeds could be better prescreened in future experiments. Overall, however, given the low cost of recruiting subjects, a feasible solution could be to just accept a substantial rejection rate.

As the study took place in the participant's home, the experimental context for each participant differed. We directed caregivers on how to seat their child for the experiment, however we did not specify details relating to the environment of which it should be carried out in. We recognized in parts of the webcam video that there were occasional distractors present in the room (i.e. toys, other people, telephone, television), which potentially could have added noise to our measures. Also, as the caregivers were aware of the movie content, although they were asked to remain still they may have given unintentional cues to their infant. Furthermore, we did not have control of the screen size or specify the child's viewing distance from the computer, likely affecting the stimulus visual angle, and possibly adding further noise. To add, we obtained a moderate kappa value (Viera & Garrett, 2005). While such value could be attributed towards both coders being relatively new to video annotating, the study's unconstrained viewing procedure could have made quantifying looking behavior more subjective than studies completed in the laboratory.

The opportunity to record webcam made employing a looking time paradigm possible. In the laboratory, looking time paradigms have been widely used to study a variety of domains in infants such as intentionality (Hamlin, Wynn, & Bloom, 2007; Woodward, 1998), emotion (Montague & Andrews, 2001; LaBarbera, Vietze, & Parisi, 1976) and speech preference (Maye, Werker, & Gerken, 2002; Cooper & Aslin, 1990). Having shown in this study that behavior can be easily captured, reviewed and quantified, this opens up the possibility of putting similar paradigms and lab-based studies that use comparable equipment on MTurk. This is not to say that all studies can be employed online, as some require specific equipment not readily available and hence require local testing, however we suggest that select tasks have the potential of being administered online.

Conclusions

In conclusion, our study demonstrates that MTurk is a powerful new tool for recruiting infant populations. We designed an online study able of capturing infant behavior directly and in particular, one that informed us of stimulus features in movies that infants were most engaged by. Online infant testing could reduce the high costs experienced in running experiments in the laboratory, and by removing barriers to larger samples, this could lead to increasing data reproducibility.

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Chapter 3: Adult and Infant Functional Imaging

Introduction

Executive function (EF) is critical for the conscious selection, analysis and integration of information from the environment. It encompasses skills such as working memory, impulse inhibition, task switching, decision-making, error correction and attention, which enable us to interact with our surroundings in an effective and purposeful way. A network of brain regions is thought to be critical for EF, the executive control network (ECN) consisting of the dorsolateral prefrontal cortex (dlPFC), inferior parietal lobule (IPL), anterior cingulate cortex (ACC), and anterior insula cortex (AIC) (Gao & Lin, 2012; Niendam et al., 2012; Cole & Schneider, 2007; Duncan & Owen, 2000).

There is controversy on when EF emerges in infancy. One perspective is that it emerges later in the first year, aligning with the development of some anatomical markers in the prefrontal cortex (Anderson, 2002; Diamond, 2002; Diamond & Goldman-Rakic, 1989). Drawing parallels between primate dlPFC lesion studies and infant performance on tasks (i.e. A-not-B task) that involve individuals reaching towards an object hidden in two possible locations following a delay, it has been suggested that rudimentary signs of working memory and inhibitory responses begin to surface between 10- and 12-months of age (Diamond 1985). However, Diamond and colleagues (1985; 1989a,b,c) noted that infants younger than 7.5-months were unable to reach for the hidden object indicating that these tests were not appropriate for younger infants, as they lacked other (non-EF) skills such as coordinated motor function, proprioception, and visuomotor control. An alternative perspective therefore is that EF may actually begin much earlier in the first year (Cusack, Ball, Smyser, & Dehaene-Lambertz, 2016). In support of this claim, it is argued that EF is particularly crucial when in an unfamiliar environment and performing new tasks. Cusack et al. (2016) explains that the absence of behavioral evidence for EF in younger infants may be because they are in a “dual-task” scenario, being distracted by the complexity of the environment such that they cannot perform concurrent psychological tasks. Furthermore, resting-state neuroimaging studies have demonstrated that the ECN is present at term birth (Doria et al., 2010).

However, while the ECN is present, we do not know if it is functioning or not. As measuring behavior is challenging, a promising strategy is to try to capture a signature of EF using neuroimaging of the brain while infants are presented with a rich, engaging stimulus. Specifically, we decided to employ naturalistic stimulation – playing a movie in the scanner – which has become increasingly popular due to its ability to capture the rich cognitive processes engaged by real world conditions. Despite the unconstrained task of passive movie viewing, in a number of studies in adults it has been shown that it evokes highly similar and synchronized neural activity across different individuals in sensory networks and regions associated with higher cognition including the ECN (Vanderwal, Kelly, Eilbott, Mayes, & Castellanos, 2015; Naci, Cusack, Anello, & Owen, 2014; Hasson, Malach, & Heeger, 2010; Jääkeläinen et al., 2008; Hasson, Nir, Levy, Fuhrmann, & Malach, 2004). Moreover, movies have a particular advantage of being highly engaging. As infants may be experiencing implicit dual task competition, by having evocative stimuli, attention will be captivated, ensuring that EF reserves are being allocated towards processing the movie.

In addition, employing dynamic, naturalistic stimuli can reduce motion that children exhibit in the scanner. During clinical scans, movies are often shown to children undergoing MRI scans to help reduce movement and to avoid the need for sedation or anesthesia (Vanderwal et al., 2015). Cantlon and Li (2013) reported that children ages 4- to 11-years old showed less head motion while viewing a movie than during a subset of matching tasks. Likewise, Vanderwaal and colleagues (2015) showed reductions in motion during naturalistic viewing compared to rest.

Therefore in an attempt to quantify EF processes, we employed functional magnetic resonance imaging (fMRI) and a naturalistic paradigm to assess the ECN functionality in the first year. Prior to testing infants, we presented a set of children-directed movies to adults during fMRI to identify the one that evoked the most robust activity in the ECN. This was then presented to infants, and the infant time-series was compared to the adult response to determine how mature the infant networks were functioning.

Experiment 1: Adult Functional Imaging

We hypothesized that if movies could evoke ECN activity in adults that we would have a greater likelihood in observing a neural response in infants. Thus the goal of this experiment was to identify which of a set of movies shown to be engaging to infants would evoke the strongest ECN response in adults.

Methods

Participants

Ten healthy adult volunteers (5 females, 5 males; *M* = 20.9 years, range = 19-23 years) participated in the study. Data from three of the adult participants were not included in the analysis because of either excessive motion (*n*=2) or incomplete data (*n*=1). All adults had normal or corrected vision, were right-handed and had no history of neurological disorders. Informed written consent was provided by all adults and they were remunerated for their time. Ethical approval was obtained from the Western University's Health Sciences Research Ethics Board (see Appendix B).

Stimuli and Design

The adults were scanned first on the top five movie clips that evoked the highest amount of visual attention in our previous experiment (see Chapter 2). These movies included: *Baby Einstein* (605 s), *Despicable Me* (681 s), *In the Night Garden* (735 s), *Teletubbies* (553 s) and *Timmy Time* (580 s). Adults watched each movie and were asked to follow it as closely as possible. The presentation order of the movies was counterbalanced. That is, across participants, the order of movies was shown in the forward and reverse sequence such that each movie was equally represented at every ordinal position. Stimuli were presented at a size of 20 degrees of visual angle, using Matlab (Nantick, MA) and the Psychtoolbox (Pelli, D. G., 1997).

Participants were made comfortable by laying supine in the scanner. Passively noise attenuating headphones were used for sound delivery and videos were watched by looking upward into a mirror box to view the projection screen behind the participant's head. All subjects were positioned inside the head coil and padding was used to restrict head movement.

MRI Protocol

fMRI Data Acquisition

Scanning was performed using a 3 Tesla Siemens Prisma system at the Robarts Research Institute in London, Ontario, Canada. The 20-channel head coil was used, as due to infants short neck and the need for ear defenders, they would not fit into the smaller 32- or 64- channel coils. Functional imaging was acquired using the Centre for Magnetic Resonance Research (CMRR, Minnesota) simultaneous multi-slice T_2^*-weighted gradient echo planar imaging (EPI) (matrix size 66x66, voxel size: 3 x 3 x 3mm, 36 slices, interslice gap of 10%, echo time (TE) = 40 ms, repetition time (TR) = 780 ms, flip angle (FA) = 54 degrees, multiband acceleration=4). An anatomical scan was acquired using a T1-weighted 3D Magnetization-Prepared Rapid Acquisition Gradient-Echo (MPRAGE) sequence (20-channel coil, matrix size = 240x256, voxel size: 1 x 1 x 1 mm, TE=2.98 ms, TR = 2300 ms, FA = 9 degrees).

Data Analysis

SPM Preprocessing

Imaging data was preprocessed and analyzed using SPM12 (Wellcome Institute of Cognitive Neurology, www.fil.ion.ucl.ac.uk/spm/software/spm12) and the automatic analysis pipeline software (Cusack et al., 2015). Preprocessing steps involved motion correction and co-registration of the EPI mean with the structural image. Non-linear warping of the individual's brain to the Montreal Neurological Institute template brain (MNI-152) was done using SPM12 normalization. The data were then smoothed with kernel of 10 mm full-width half-maximum (FWHM), and the time-series in each voxel was high pass-filtered with a cutoff of 1/128Hz to remove low-frequency noise.

Cross-subject Correlation and Region of Interest (ROI) analysis

We performed a whole-brain leave-one-out intersubject correlation (ISC) analysis, to visualize whether similar brain activity was evoked in different adults watching the same movie. For each movie, we correlated the time-course at each voxel of each adult with the mean time-course of all other adults at that voxel. Therefore, each adult had five whole brain r-maps representing their mean similarity to the other adults for each of the five movies viewed. Subsequently, the r-maps of each movie across adults were averaged to obtain a mean r-map for each movie. The whole brain analysis was used to visualize the results and arbitrary thresholded at r=0.1.

To quantify the ISC in particular brain networks, and to perform statistical analyses, we extracted the time-courses during movie viewing in a set of regions-of-interest (ROIs) taken from Shirer et al. (2012) (Figure 6). Networks included: primary visual cortex (V1), higher visual, auditory, sensorimotor, language, basal ganglia, visuospatial, anterior salience network, posterior salience network, precuneus, dorsal default mode network (dDMN), ventral default mode network (vDMN), left ECN (lECN) and right ECN (rECN). Realignment parameters were then used to regress out movement related artifacts in each of the participants' time-series from each ROI.

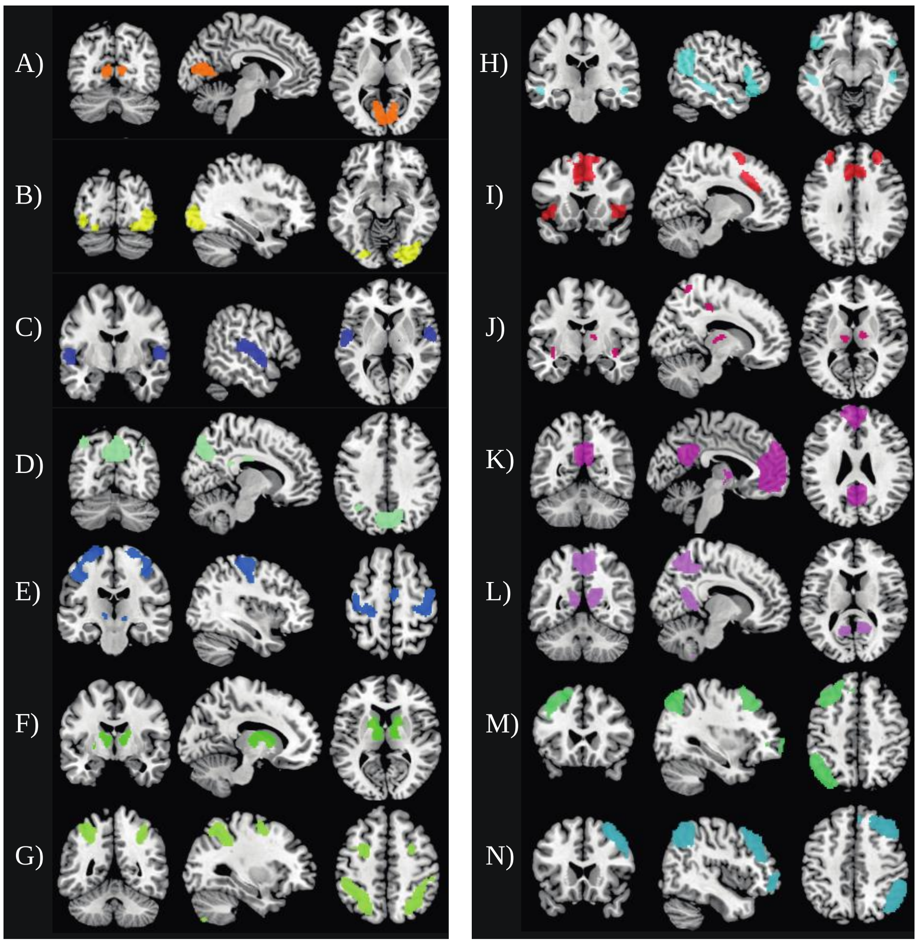

Figure 6. Location of ROI networks: A) V1, B) higher visual, C) auditory, D) precuneus, E) sensorimotor, F) basal ganglia, G) visuospatial, H) language, I) anterior salience network, J) posterior salience network, K) dDMN, L) vDMN, M) lECN, and N) rECN.

For each movie and ROI, the ISC was calculated in a similar way as for the whole brain analysis, and then tested for significance. We did not use parametric statistics (e.g., a random effects t-test on the correlation values) as due to the leave-one-out cross validation, the correlation values of the different adults are not independent. Instead, a null distribution of the mean ISC for each network was generated by conducting a nonparametric permutation test. This involved randomly rotating the ROI time-series of each subject so that different subjects were no longer aligned with each other in time, and then applying the same ISC analysis methods as described above. This process was repeated 10,000 times for each ROI and movie. The position of the true ISC value relative to this null distribution was then used to determine significance. We hypothesized *a priori* that all movies would evoke activity in sensory (V1, higher visual and auditory) and executive networks. For these planned comparisons, we report uncorrected p-values thresholded at $p < 0.05$. For the remaining 9 networks, we report results following Bonferroni correction for multiple comparisons at $p < 0.05$. As negative ISC within a group is not interpretable, one-tailed tests were used.

Results

Figure 7 shows whole-brain ISC across adults during viewing of the five movies. At this threshold, all movies evoked activity in a number of expected regions, such as auditory cortex on the superior temporal plane, and in visual cortex in the occipital lobe. Furthermore, one movie (*Despicable Me*) was found to evoke substantially more widespread activity, stretching into the frontal and parietal lobes.

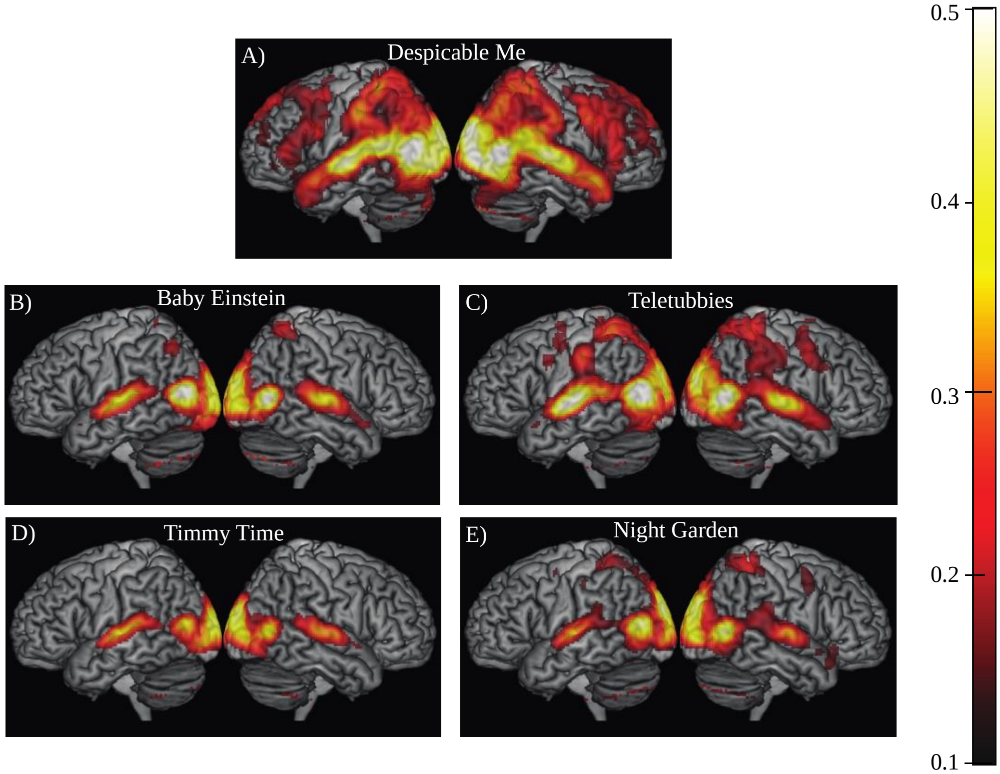

Figure 7. Average leave-one-out whole brain ISC maps across movie, thresholded at r=0.1.

The ROI analysis showed that within all movies synchronizations were statistically reliable in sensory regions including V1, auditory and higher visual networks (all $p<0.05$) (Figure 8, Table 3). *Despicable Me* displayed significant ISC in the basal ganglia, bilateral ECN, language, precuneus, visuospatial, vDMN and dDMN networks (all $p<0.05$) (Figure 8A). *Baby Einstein* showed high ISC in the lECN and precuneus (Figure 8B) while *Teletubbies* showed posterior salience network and vDMN (all $p<0.05$) (Figure 8C). Lastly *Timmy Time* (Figure 8D) and Night Garden (Figure 8E) did not reveal any additional significant networks.

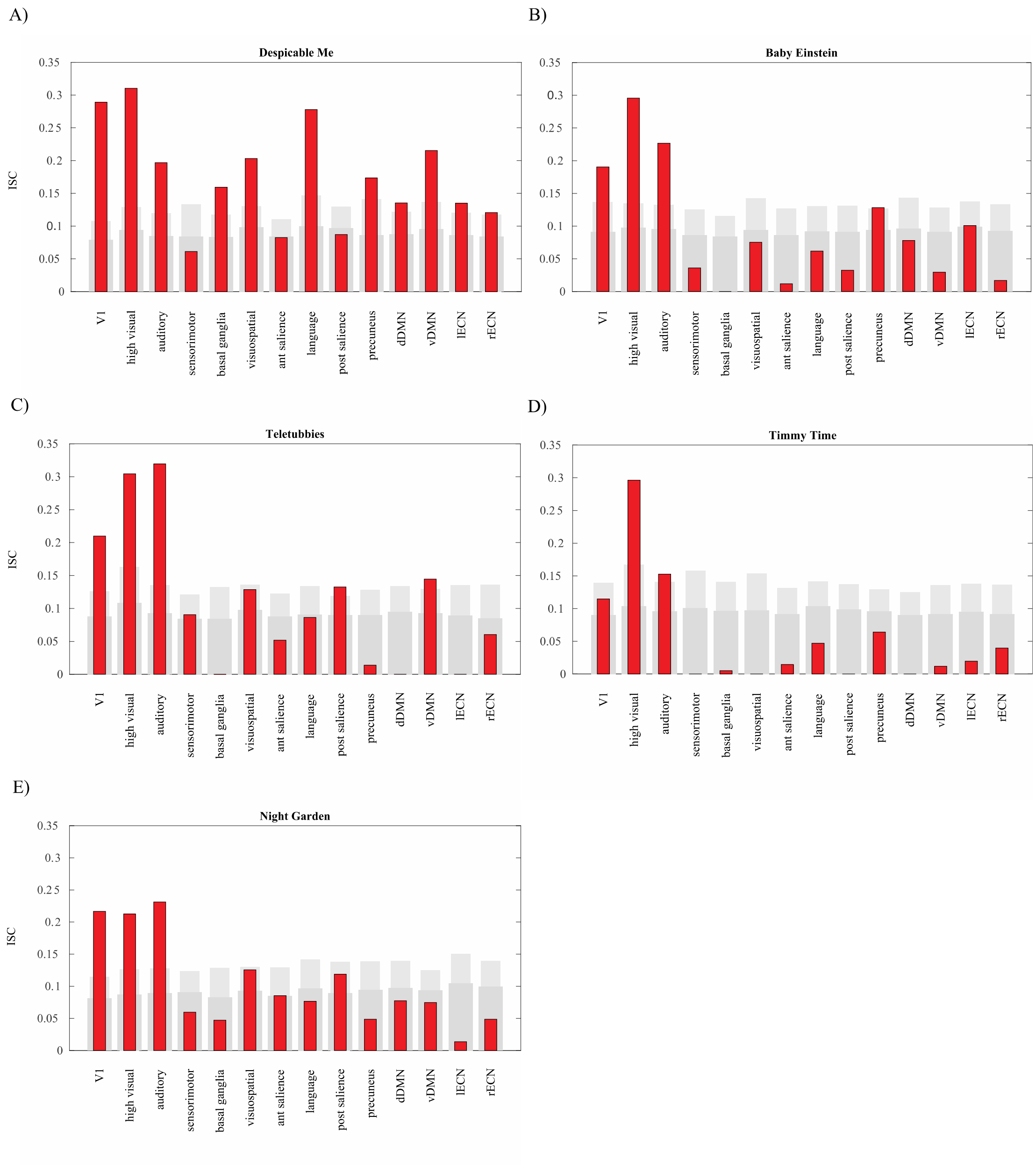

Figure 8. ROI analysis of adult-to-adult ISCs across movies. Taller grey bars represent bonferroni-corrected thresholds (p<0.05). Shorter grey bars represent uncorrected thresholds ($p < 0.05$).

Table 3.

ROIs with significant ISC across movies.

Movie	ROI	*r*	*p*-value
Baby Einstein	V1	0.19	0.001
	High visual	0.30	0.001
	Auditory	0.23	0.001
	Precuneus	0.13	0.003
	lECN	0.10	0.046
Despicable Me	V1	0.29	0.001
	High visual	0.31	0.001
	Auditory	0.20	0.001
	Basal ganglia	0.16	0.001
	Visuospatial	0.20	0.001
	Language	0.28	0.001
	Precuneus	0.17	0.001
	dDMN	0.14	0.001
	vDMN	0.22	0.001
	lECN	0.13	0.001
	rECN	0.12	0.003
Night Garden	V1	0.22	0.001
	High visual	0.21	0.001
	Auditory	0.23	0.001
Timmy Time	V1	0.11	0.013

	High visual	0.30	0.001
	Auditory	0.15	0.002
Teletubbies	V1	0.21	0.001
	High visual	0.30	0.001
	Auditory	0.32	0.001
	Post salience	0.13	0.001
	vDMN	0.14	0.002

Note. V1, higher visual, auditory and executive networks were thresholded at uncorrected $p<0.05$. The remaining 9 networks were Bonferroni corrected for multiple comparisons at $p<0.05$.

Discussion

Experiment 1 assessed adult brain responses to a set of children-directed movies. Across all movies, we found high ISC in V1, higher visual and auditory networks, aligning well with our hypothesis. The recruitment of higher associated regions such as the ECN were observed, however to a lesser extent across movies than sensory regions as only bilateral activity was observed in *Despicable Me* and left lateralized activity was seen in *Baby Einstein*. Overall, there were striking differences in the observed activation across movies, demonstrating that some were much more effective than others (Hasson, Malach, & Heeger, 2010; Hasson et al., 2008).

Differences in the strength of ISC between movies may have been due to extent to which they contained coherent storylines, as it has been argued that these are likely to recruit frontal cortices because of the executive engagement required to follow and understand the plot (Naci et al., 2014). *Despicable Me* was oriented at an wider audience including toddlers that are widely perceived to be able to attend and problem solve to some degree, and thus be executively engaged. However, at present it is unknown whether young infants can also be engaged in this way. As we were able to find a movie capable of evoking reliable and strong time course activity in the ECN bilaterally, our next step was to then test this movie in infants.

Experiment 2: Infant Functional Imaging

In this experiment we tested whether a movie found to engage infants' attention (Chapter 2), and to evoke reliable ECN activity in adults (Experiment 1), would engage the ECN in infants.

Methods

Participants

Seven typically developing infants (5 females, 2 males; M = 5.85 months, range = 3.4-8.03 months) participated in the study. Informed written consent was provided by the infant's caregiver prior to the study commencing. Ethical approval was obtained from Western University's Health Sciences Research Ethics Board (see Appendix C).

Of the infants, four participants were excluded due to excess motion or lack of compliance. This success rate (43%) is comparable to the success rate for the more common scanning of infants in natural sleep, and is very encouraging. Three infants across a range of ages (3-, 6- and 8-months) entered the final analysis.

Procedure

Infants were swaddled in loose cotton sheet by a parent or by a neonatal nurse, to calm the infant and to reduce movement. The infant was then positioned in the head coil looking upward into a mirror box to view the projection screen. A researcher accompanied the infant into the MRI, taking a sphinx position and cradling their arms to maintain physical contact with the baby and to calm them to further discourage motion. In addition to the noise-attenuating headphones, earmuffs were worn to protect the infants' hearing. Infants were given a non-metallic pacifier when a parent recommended it. Leading up to the scan, continuous movie stimuli was presented to keep the infant engaged.

Infants were monitored throughout the scan by a MR-compatible infrared camera and a noise-cancelling microphone placed inside the magnet bore. Heart rate and oxygen saturation were monitored using a neonatal monitoring probe placed on the infant's foot (Fibre Optic Pulse Oximeter; Nonin Medical, Plymouth, Minnesota). Once the infant was calm, scanning would commence and *Despicable Me* would play. fMRI data acquisition followed the same protocol as Experiment 1.

Data Analysis

The preprocessing procedures from Experiment 1 were again used here. If the infant fell asleep, their time-series was truncated to coincide with awake periods. Each infant underwent a variant on the ISC analysis that allows comparison of individuals to a control group. Pairwise correlations were taken between each infant and each adult to produce a mean infant-to-adult r-map. Given the small number of infants and their wide age range, we did not perform infant-to-infant ISC. We then used the same ROI analysis as in the adult study. Again, a null distribution generated by rotating the adult time-series was used to determine the significance. However, as negative ISC is interpretable when comparing two distinct groups, testing was two-tailed.

Results

Each infant underwent ISC analysis with their volumes truncated as follows: 3-month old infant (480 volumes, 374.4 s), 6-month old infant (180 volumes, 140.4 s) and 8-month infant (780 volumes, 608.4 s). In the 3-month old infant, significant positive synchronizations with adults were seen in high visual and interestingly, the lECN (all $p<0.05$) (Figure 9A). This is a promising proof-of-principle, that the ECN can be evoked in infants by rich engaging stimuli. However, surprisingly, the 6-month old infant displayed significant negative ISCs with adults in high visual, auditory, basal ganglia, and in the lECN (all $p<0.05$) (Figure 9B). Negative hemodynamic responses have been reported before in infant neuroimaging (Altman and Bernal, 2001; Anderson et al, 2001; Kozberg, Chen, DeLeo, Bouchard & Hillman, 2013; Yamada et al., 2000; Born et al., 1998;), but this is certainly not a universal finding and others have suggested more typical responses (Arichi et al 2012). The 8-month old infant to adult ISC demonstrated significant positive correlations in V1 ($p<0.05$) and positive correlations bilaterally in the ECN of the 8-month old, however this effect did not reach statistical significance (Figure 9C).

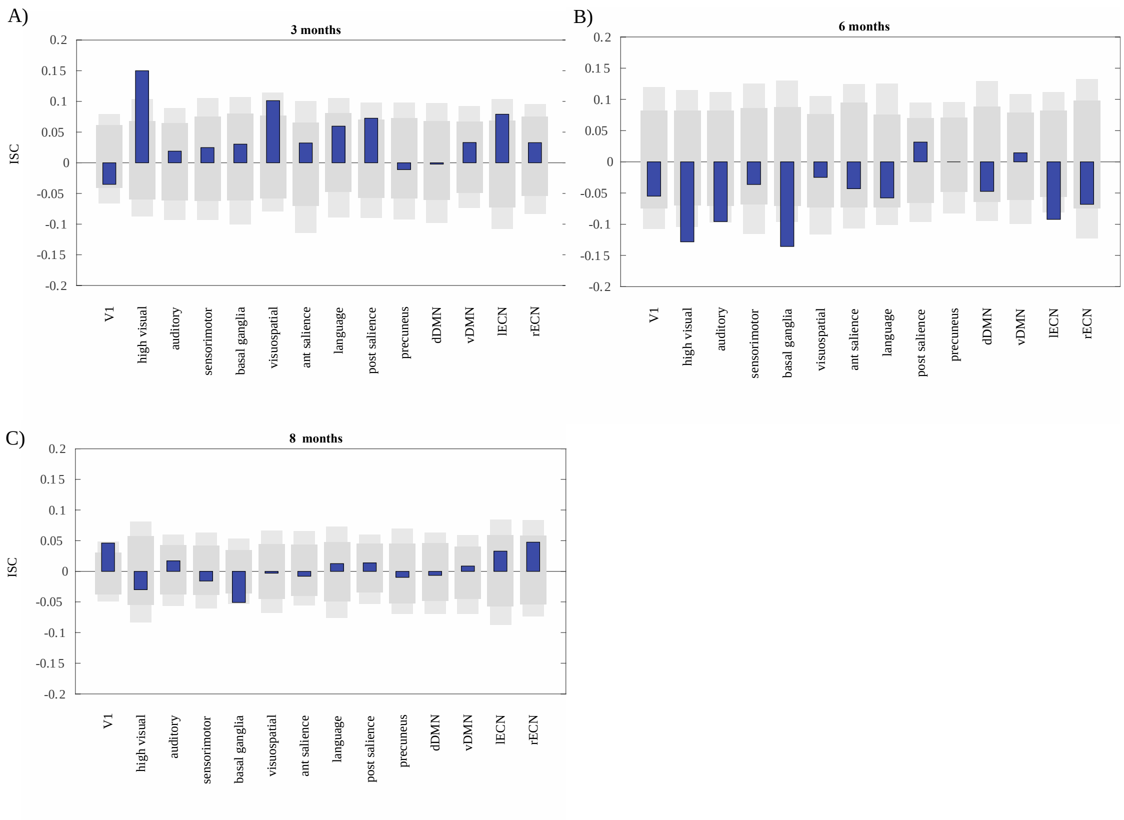

Figure 9. ROI analysis of infant-to-adult ISCs in response to viewing *Despicable Me*. Taller grey bars represent bonferroni-corrected thresholds (p<0.05). Shorter grey bars represent uncorrected thresholds ($p < 0.05$).

Discussion

We developed a novel method to examine the emergence of EF in infants. As we saw in Experiment 1 that *Despicable Me* evoked high ISC in more networks than any other movie and was the only video to reliably elicit bilateral ECN activity in adults, we transferred this movie into infant functional imaging. Here, we demonstrated that a 3-month old infant expressed ECN activity in the left hemisphere similar to that of adults. Positive correlations between infants and adults in the ECN were observed in the 3- and 8-month old infants, however the trend was reversed in the 6-month old infant.

Aligning with Cusack et al. (2016), we found that infants might potentially have EF much earlier than previously reported in behavioral research. We showed evidence of functional processing in the ECN in a 3-month old infant comparable to that of adults, suggesting that the infant's ECN may be undergoing similar mechanisms as adults to process the movie. While it may be that infants are too distracted by the unfamiliar environment to show any sophisticated EF behavior, this hypothesis still remains to be tested.

In addition, we observed a negative activation in the ECN by the 6-month old infant. Concurring with previous studies that have employed fMRI and external methods to evoke regional brain activity, inconsistent patterns of polarity in the blood oxygenated level-dependent (BOLD) have been reported during infancy and in cross sample comparison between infants and adults. Born and colleagues (2002) showed that upon visual stimulation, negative BOLD signals were observed in sleeping adults, similar to that seen in sedated (Seghier, et al., 2004; Yamada, 2000) and non-sedated children (3 days to 48 months) (Born, 1998). Likewise, sedated (Altman & Bernal, 2001) and non-sedated sleeping newborn infants (Anderson et al., 2001) have also demonstrated contrasting responses with adults, showing negative activity in primary auditory cortex when presented with auditory stimuli while asleep. Seeing that sedation alone did not cause the signal decrease, these studies suggest that factors such as wakefulness may be influencing the polarity of the signal. In our study, we recorded video while infants were being scanned and restricted our analyses to periods of when the infant was awake. Considering that the 6-month old had the shortest time-series and fell asleep soon after the movie commenced, the child may have been in a less alert state compared to the other infants, giving rise to the reverse trend. While the infant's awake state was subjectively determined by the researcher, additional measures should also be incorporated in the future to objectively determine wakefulness such as electroencephalography (EEG). However given the complexity of scanning awake infants, this would require some development to create protocols that are feasible.

Additionally, inconsistent findings across infant groups may have been due to the developmental differences in the hemodynamic response. In adults, the morphology of the hemodynamic response function (HRF) has been well characterized and replicable, however only few studies have investigated it in infants (Aslin, 2015). Described as smaller in amplitude and delayed in time compared to adults (Cusack et al., 2016, Aslin, 2015; Arichi, 2012; Seghier et al., 2004) such contrasts have been suggested as being a result of immature vascular regulation and myelination in infants (Minagawa-Kawai et al., 2010). Substantial changes that occur in the neurovascular coupling during early infancy have been implied in contributing towards the variability in the hemodynamic response in infants across brain regions and ages (Aslin, 2015; Kozberg et al., 2013; Arichi, 2012). Specifically, cerebral blood flow (CBF), a parameter known to highly influence the HRF, has been shown to be particularly low in infants compared to adults (Aslin, 2015; Seghier et al., 2003; Altman and Bernal, 2001). It has been hypothesized that in response to experimental stimulation, due to low CBF expression in infants, oxygenated hemogloblin demands may not be compensated, leading to a less detectable infant HRF and the possibility of a negative BOLD response occurring (Aslin, 2015; Arichi, 2012 ; Seghier et al., 2003). Furthermore, apparent differences may involve changes in cerebral vessel and volume density from infancy to adulthood, explaining for faster CBF responses with age and increased regional activity (Arichi, 2012; Seghier et al., 2003). Additional studies are required to further understand the changes of oxygen metabolism and hemodynamic response such that reliable functional responses in infants can be identified.

Data truncation could have also attributed to the different patterns of ECN activity observed across infants. As previously mentioned, all infants underwent individual time-series truncation to align the fMRI data to their state of wakefulness. Given the changed time-series, strength of signal between infants was likely different and particularly weak in the 6-month old infant who had their times-series cut by one-fifth. Moreover, movement may have likely played a role in the heterogeneous findings. As mobility and behavioral report become more explicit with age, more motion may have been exhibited in the older infants giving rise to indiscernible ECN activity in the 6- and 8-month old.

Lastly, ECN activity may not have been consistent across infant groups due to their lack of engagement with parts of movie. It should be noted that the movie was chosen based on whether it evoked ECN neural responses in adults. As adults have been shown to be evoke the ECN to films that contain narratives, this may not apply to infants. An intriguing possibility is whether a more infant oriented stimulus that contained content more familiar to infants or lacked narrative content would result in greater consistency among infants.

Our study involved an audiovisual stimulus, which necessitated infants to remain awake. While infants younger than 3-months of age have been scanned awake in the past (Biagi, Crespi, Tosetti, & Morrone, 2015; Dehaene-Lambertz et al., 2009; Dehaene-Lambertz et al., 2002), we demonstrated that a movie-fMRI paradigm was a good means in gauging older cohorts. To prepare infants for the scan, we mailed caregivers a CD of MRI sounds that their infant would hear during the scan and asked them to play it twice daily. In addition, we recommended that parents practice with their child lying on their back while viewing screen media on either an Ipad or cell phone. This was suggested to simulate the conditions that their infant would experience in the scanner. Techniques that we employed on testing day involved having constant sensory stimuli playing (i.e. another movie) while the infant was being set up on the scanner bed and having a researcher hold the infant throughout the scan. In combination of practicing the MRI protocol before the scan and generating a comfortable environment for the infant during the scan, we believe that this aided in our high success rate in collecting data from three of the seven participants.

We report a new method of studying infant EF development without the need of an explicit task. By using naturalistic stimuli combined with fMRI, we revealed a significant positive ECN activity in a 3-month old that coincided with the adult response. In contrast, the 6-month old infant had a negative response, while the 8-month old exhibited positive correlations in the ECN. Given the small number of infants analyzed, our next step is to recruit more infants in order to elucidate and draw conclusions regarding whether infants express a functioning ECN.

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Chapter 4: General Discussion

We tested the hypothesis that executive function (EF) begins early in the first year, rather than later as previously found with behavioral tasks (Diamond & Doar, 1989; Diamond & Goldman-Rakic, 1989; Diamond, Zola-Morgan, & Squire, 1989; Diamond, 1985). We combined naturalistic stimuli with functional magnetic resonance imaging (fMRI) to examine the functional development of the executive control network (ECN). This novel approach demonstrated a new means of assessing infants without the need for an explicit task. In addition, we discovered that naturalistic paradigms led to a manageable small degree of motion in the scanner. By engaging infants in a comfortable environment, we successfully scanned them awake and captured brain responses indicative of naturalistic cognitive processing.

To carry out this study using a naturalistic paradigm, we required a movie capable of sustaining infants' attention and limiting motion. To choose the stimuli, we ran an online study on Mechanical Turk (MTurk) to identify movies that were engaging to infants aged 5- to 8-months. We employed a looking time paradigm using the participant's webcam to quantify the infant's attention towards one of ten child-directed movies. We found that regardless of age, infants were engaged by some movies more so than others. To determine what parts of the movie were driving infant's looking behavior, we further examined the top five movies (*Baby Einstein*, *Despicable Me*, *In the Night Garden*, *Teletubbies* and *Timmy Time*) that evoked the highest proportion looking times and annotated them for production elements typically found in infant television programs. We found that the presence of faces, singing and rhyming and camera zooms increased infant attention.

Seeing that these movies were effective in attracting infants' attention, we then transferred them into adult functional imaging to establish which movie evoked strong ECN responses. We used intersubject correlation (ISC) analysis to determine how synchronized the brain activity of adults were to one another and assessed the ECN along with several other networks. While similar networks were evoked across all movies, namely sensory regions (primary visual, higher visual and auditory networks), each movie expressed a distinct correlational brain map. Most importantly, *Despicable Me* was the only movie to evoke high bilateral ISC in the ECN in adults. Using the adult time-series as the maturational benchmark for infants, we transferred this movie into infant functional imaging. The 3-month old infant expressed ECN activity in the left hemisphere similar to that of adults while the 6-month old demonstrated negative activity. In the 8-month old infant, positive ECN activity was observed.

As previously mentioned, we speculated that inconsistent findings across infants might have been due to differences in the infant's state of wakefulness. This has been shown to be associated with negative activations in adults (Born et al., 2002) and infants (Altman & Bernal, 2001; Anderson et al., 2001:Yamada et al., 2000; Born et al., 1998) while sleeping. As we did not objectively measure alertness, this may have explained for the reverse ECN response observed in the 6-month old.

Differences in the hemodynamic response between infants and adults could have also contributed towards the heterogeneous findings. Maturational factors in neurovascular coupling known to influence the hemodynamic dynamic response such as CBF and cerebral vessel size, suggest that negative blood oxygenated level-dependent (BOLD) signals are a result of the cerebral vasculature inability to compensate for the deoxygenated haemoglobin (Aslin, 2015; Arichi, 2012). Therefore, the immature vasculature may explain for the changes in BOLD signal polarity across our infant cohorts.

As we showed in our behavioral study, movie sequences containing faces, camera zooms, and singing and rhyming in particular increased their attention. Given that attention was required in order to perceive the movie, parts that did not contain aspects interesting to infants may have resulted in infants ignoring the stimuli, leading to the lack of and/or inconsistent ECN signal observed in our findings. In addition, the movie that evoked the highest attentional engagement was not employed in functional imaging. Although *Despicable Me* was not significantly worse at maintaining attention than any of the other movies, numerically it was the fourth best movie. Therefore it is quite possible that a movie even more effective of attracting the infants' attention could also engage the ECN. In addition, the level of comprehension towards the content may have also been a factor in the variable ECN activity found across infants. While it has been argued that infants attend to media that does not exceed their understanding (Anderson & Pempek, 2005;Valkenburg & Vroone, 2004), the relation between attention and comprehension during infancy presents a major challenge. In the future, employing stimuli that is more familiar to infants may present greater consistency and perhaps more attentional engagement more fitting for functional imaging. Moreover, although *Despicable Me* evoked reliable ECN activity in adults, this did not necessarily mean that activity towards the same stimulus would be observed in infants. As a first approximation to make our project practical, we hypothesized that if the stimulus could evoke the ECN in adults, we would have a greater likelihood in observing neural activation in infants. It is possible that this simplifying assumption is not correct, and that a movie that evokes less ECN activity in adults might evoke the most in infants. Following our proof-of-principle, a future, larger research project could test for this dissociation.

Past studies that examined EF in infants used behavioral paradigms that were not practical in younger infants. Here we show for the first time, promising evidence that a functional ECN may be present in infants as young as 3-months of age, however, to substantiate this claim, more infant testing is needed. Also, further studies are required to determine what drives ECN activity. Similar to our MTurk study, future work could associate movie annotations with the ROI time-series. This would allow us to discriminate what parts of the movie are modulating these networks and shed light on their functional specificity. Moreover, we invite the use of eye tracking in tandem with imaging to assess the influence of looking strategy with regional brain activity. As infants could be looking at different locations of the visual scene and hence be interpreting the stimuli differently, this could clarify whether the same visual scene is actually evoking the network. Lastly, to test whether the ISC in the ECN during movie viewing actually represents executive elements of the movie, we anticipate to record the moment-by-moment executive demands through employing the dual-task paradigm developed by Naci et al. (2014).

The biggest challenge in acquiring informative fMRI data in pediatric populations is finding techniques that can limit participant motion. With such difficulties heightened in scanning awake infants, this can explain for why so few studies have been reported (Biagi, Crespi, Tosetti, & Morrone, 2015; Dehaene-Lambertz et al., 2009; Dehaene-Lambertz & Dehaene, & Hertz-Pannier, 2002). To circumvent this barrier, we developed a unique method of testing awake infants by using a naturalistic paradigm teamed with fMRI. We learned that caregivers who practiced with their infant the at-home simulation of the scanning procedure routinely were better prepared come testing day. During the scan, incorporating constant sensory stimulation and having a researcher cradle and monitor the infant throughout the scan exemplified a calming effect on the infant such that motion could be limited. Most importantly however, we ensured that the stimulus was engaging to infants prior to scanning, as shown in our MTurk study. Therefore in combination of these techniques, we believe that this led to our high success rate (43%, similar to typical sleeping infant studies) and would recommend that future researchers intending to assess awake infants follow a similar strategy.

Conclusion

This study showed that an ECN similar to that of adults might emerge in 3-month old infants and follow different trajectories across the first year. We developed a novel method effective at scanning awake infants and capable of measuring functional repertoire without the need of an explicit task. Taken together, we provide a powerful tool for potentially measuring EF in young infants and one that may be suitable for addressing basic questions regarding conscious perceptual development and awake fMRI in early childhood.

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Appendix A: Mechanical Turk Ethics

Research Ethics

Western Research

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Rhodri Cusack
File Number: 102986
Review Level: Delegated
Approved Local Adult Participants: 0
Approved Local Minor Participants: 0
Protocol Title: Web testing of infants less than one-year old
Department & Institution: Social Science\Psychology,Western University
Sponsor:
Ethics Approval Date: July 24, 2013 **Expiry Date:** December 31, 2013
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	Revised protocol	

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]

Ethics Officer to Contact for Further Information

___ Erika Basile (ebasile@uwo.ca)	✓ Grace Kelly (grace.kelly@uwo.ca)	___ Vikki Tran (vikki.tran@uwo.ca)	___ Shantel Walcott (swalcot@uwo.ca)

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London, ON, Canada N6A 3K7 t. 519.661.3036 f. 519.850.2466 www.uwo.ca/research/services/ethics

Appendix B: Adult Functional Imaging Ethics

Research Western

Use of Human Participants - Ethics Approval Notice

Principal Investigator: Dr. Rhodri Cusack
File Number:101988
Review Level: Delegated
Approved Local Adult Participants:50
Approved Local Minor Participants:0
Protocol Title: Neural mechanisms of visual and auditory perception, short-term memory, and imagery - 18625E
Department & Institution: Social Science\Psychology,Western University
Sponsor:
Ethics Approval Date: February 02, 2012 **Expiry Date:**December 31, 2016
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	Revised study methods. Scanning will now be done with a 7Tesla scanner in stead of the 3Tesla originally approved.	
Revised Letter of Information & Consent		2011/11/04

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer to Contact for Further Information

Janice Sutherland (jsutherl@uwo.ca)	✓ Grace Kelly (grace.kelly@uwo.ca)	Shantel Walcott (swalcot@uwo.ca)

This is an official document. Please retain the original in your files.

The **University** *of* **Western Ontario**
Office of Research Ethics
Support Services Building Room 5150 • London, Ontario • CANADA - N6G 1G9
PH: 519-661-3036 • F: 519-850-2466 • ethics@uwo.ca • www.uwo.ca/research/ethics

Appendix C: Infant Functional Imaging Ethics

Western Research

Research Ethics

Western University Health Science Research Ethics Board
HSREB Amendment Approval Notice

Principal Investigator: Dr. Rhodri Cusack
Department & Institution: Social Science\Psychology,Western University

HSREB File Number: 103665
Study Title: Developing assessments of perinatal brain injury using fMRI
Sponsor:

HSREB Amendment Approval Date: November 21, 2014
HSREB Expiry Date: April 30, 2018

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Revised Western University Protocol	Received Nov 14, 2014	
Revised Letter of Information & Consent	controls	2014/11/14
Revised Letter of Information & Consent	NAS participants	2014/11/14
Revised Letter of Information & Consent	Patients	2014/11/14
Instruments	Drug use questionnaire	2014/11/14

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Amendment Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review. If an Updated Approval Notice is required prior to the HSREB Expiry Date, the Principal Investigator is responsible for completing and submitting an HSREB Updated Approval Form in a timely fashion.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer to Contact for Further Information

Erika Basile ebasile@uwo.ca	Grace Kelly grace.kelly@uwo.ca	Mina Mekhail mmekhail@uwo.ca	Vikki Tran vikki.tran@uwo.ca

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Western University, Research, Support Services Bldg., Rm. 5150
London, ON, Canada N6A 3K7 t. 519.661.3036 f. 519.850.2466 www.uwo.ca/research/services/ethics

Curriculum Vitae

Name:	Michelle Tran
Post-secondary Education and Degrees:	The University of Western Ontario London, Ontario, Canada 2010-2014 B.Sc. The University of Western Ontario London, Ontario, Canada 2014-present M.Sc.
Honours and Awards:	Western Scholarship of Distinction: 2010 Dean's Honor List: 2011-2014 Berlin School of Mind and Brain Travel Grant: 2015 Frederick Banting and Charles Best Canada Graduate Scholarship ($17,500 per annum): 2015-2016
Related Work Experience	Teaching Assistant PSYCH 2810: Psychology Statistics 2014-2015 Teaching Assistant PSYCH 2030B: The Maladjusted Mind 2015-2016 Teaching Assistant PSYCH 2043B: Exceptional Children – Developmental Disorders 2015-2016

Publications and Contributions

Cusack, R., Stojanoski, B., Tran, M.C., Linke, A.C., & Wild, C.J. Pubmed Commons commentary on "Auditory perception at the root of language learning" http://www.ncbi.nlm.nih.gov/pubmed/23019379/#comments

Tran, M., & Cusack, R. "Does infant-directed television pump mental iron in the prefrontal cortex?" *The Organization for Human Brain Mapping, Geneva, Switzerland, 2016.*

Tran, M., Cabral., Patel, R., & Cusack R. Submitted for publication. Easy online recruitment and testing of infants with Mechanical Turk.