

## **Abstract**

Children with epilepsy may be vulnerable to impaired social attention given the increased risk of neurobehavioural comorbidities. Social attentional orienting and the potential modulatory role of attentional control on the perceptual processing of gaze and emotion cues have not been examined in childhood onset epilepsies. Social attention mechanisms were investigated in patients with epilepsy ( $n = 25$ ) aged 8-18 years old and performance compared to healthy controls ( $n = 30$ ). Dynamic gaze and emotion facial stimuli were integrated into an antisaccade eye-tracking paradigm. The time to orient attention and execute a horizontal saccade toward (prosaccade) or away (antisaccade) from a peripheral target measured processing speed of social signals under conditions of low or high attentional control. Patients with epilepsy had impaired processing speed compared to healthy controls under conditions of high attentional control only when gaze and emotions were combined meaningfully to signal motivational intent of approach (happy or anger with a direct gaze) or avoidance (fear or sad with an averted gaze). Group differences were larger in older adolescent patients. Analyses of the discrete gaze emotion combinations found independent effects of epilepsy-related, cognitive and behavioural problems. A delayed disengagement from fearful gaze was also found under low attentional control that was linked to epilepsy developmental factors and was similarly observed in patients with higher reported anxiety problems. Overall, findings indicate increased perceptual processing of developmentally relevant social motivations during increased cognitive control, and the possibility of a persistent fear-related attentional bias. This was not limited to patients with chronic epilepsy, lower IQ or reported behavioural problems and has implications for social and emotional development in individuals with childhood onset epilepsies beyond remission.

**KEY WORDS:** Gaze orienting, shared signals, emotion, saccade

## 1. Introduction

The neurobehavioural comorbidities associated with childhood onset epilepsies include neurocognitive deficits, psychiatric disorders and possible long-term difficulties with social adjustment.<sup>1</sup> Behavioural and neuroimaging work with neurodevelopmental and neuropsychiatric populations has identified aberrant integration of the social perceptual processing of gaze and emotion signals with higher order attentional control as a core mechanism underlying social impairments.<sup>2,3</sup> As yet however it is unclear whether children with epilepsy will show typical responding to gaze and emotion cues, or if impaired social attention processes are evident and associated with epilepsy related factors, cognitive deficits and behavioural problems.

Prior pediatric research on social perceptual skills remains limited and has focused mainly on patients with temporal lobe epilepsies (TLE).<sup>4</sup> Studies report aberrant face processing mechanisms<sup>5</sup> and gaze direction and emotion recognition deficits.<sup>6,7</sup> Patients often present with broader neurocognitive dysfunction, attributed to a generalized impact of early onset on neurodevelopment,<sup>8</sup> and impairment is often found across different patient groups when compared with healthy controls. Few studies have addressed the link between social perceptual skills and behavioural difficulties. Golouboff et al. reported impaired fear recognition predicted behavioural problems in a subset of TLE patients, and perceptual theory of mind deficits were shown to correlate with social and attention problems in a heterogeneous patient group with below average IQ<sup>9</sup>. Overall, findings indicate a high degree of individual variability, and deficits not isolated to the social perceptual domain. The prevalence of neurobehavioural problems in complicated and uncomplicated epilepsies is well recognized<sup>10</sup> yet the integrity of core social processes that include attentional orienting to gaze and emotion cues remains to be addressed in children with epilepsy.

Extensive research on social attention has observed facilitation of attentional orienting to locations cued by gaze, attributed to a possibly reflexive social orienting mechanism to follow others' gaze,<sup>11,12</sup> and emotion expressions are shown to differentially modulate this attentional orienting. This response modulation has been used to index skills in the perceptual decoding of facial cues that scaffold inference on communicative intent in typical and atypical populations. Notably, the potentiated attentional orienting to fear cues, interpreted as evidence of an adapted mechanism for identifying environmental threat,<sup>13</sup> as well as threat-related attentional biases implicated in the development and maintenance of anxiety disorders.<sup>14</sup> Further work has also identified gaze direction and emotional expression reciprocal interactions, whereby specific configurations (shared signals) enhance recognition when consistent with motivational intent of approach (a direct gaze with happy and anger) and avoidance (averted gaze with fear or sad).<sup>15</sup> This preferential processing of shared signals has been observed by late childhood in typical development, whereas such response patterns are reportedly absent in similar aged children with autistic spectrum disorders, leading to the hypothesis that a weakened integration of multiple social cues underlies social impairments in ASD.<sup>16</sup>

Studies have also manipulated the level of cognitive control required for a successful response in order to assess more complex cognition-emotion interactions underpinning behavioural regulation.<sup>17-19</sup> Behavioural studies report continued improvement in both emotion discrimination abilities and integration with inhibitory control processes, consistent with neuroscientific evidence of a protracted developmental course of social attention networks throughout childhood and adolescence.<sup>20-22</sup>

Children with epilepsy without global developmental delay are at risk of disrupted developmental integration of attention and inhibitory control with other domains.<sup>23</sup> It is important to determine if there is a vulnerability to the developmental integration of social

perceptual processes and cognitive control that underlies socio-emotional and behavioural regulation. The aims of the study are to compare social attentional orienting under low and high cognitive control to gaze cues and meaningful social signals, using a modified gaze emotion antisaccade eye-tracking paradigm. Analyses will compare age-related changes in social attention between patients and controls, and assess if observed deficits are associated with epilepsy-related factors, cognitive deficits and behavioural problems.

## **2. Materials and Methods**

### **2.1. Participants**

The study involved a total of 55 children aged 8 to 18 years old, 25 patients and 30 healthy control children. The inclusion criteria for patients were children with epilepsy (CWE) in mainstream education with presumed genetic or unknown etiology without identifiable structural or metabolic abnormalities. The research program's recruitment strategy has been previously described<sup>9</sup>. At recruitment to the research program a pediatric neurologist classified patients in accordance with the revised terminology proposed by the International League Against Epilepsy (ILAE) 2005-2009.<sup>24</sup> Recent classifications of drug resistant epilepsy<sup>25</sup> or resolved epilepsy<sup>26</sup> were not available at the time of recruitment to the research program. Therefore the broader terms 'chronic' and 'controlled' have been adopted here. In the present sample of children, who agreed to continue to participate in research, there were fourteen (57%) patients in receipt of antiepileptic drugs ('chronic' epilepsy) whereas eleven children were unmedicated with four who had never taken AEDs ('controlled' epilepsy). Of the eleven unmedicated children, 9 had no reported seizures in the previous 12 months. Patient IQs ranged between 60-121 with eight children in the mild intellectual disability range of 60-80 IQ points (3 children IQ <70). Table 1 displays

summary data on clinical variables and more detailed information on individual patients is reported in the supplementary materials (Table S1).

The healthy control group (HC) was recruited via a university research database. All 55 children had normal or corrected to normal vision and none had received a diagnosis of a learning disability or a neurodevelopmental disorder. No IQ estimates were collected from controls as this group was recruited from a typical population and would not have matched those patients who had a below average IQ. Participant information is displayed in Table 1.

Table 1

Participant Information

	Controls (n = 30)	Children with Epilepsy (n = 25)
Gender (M: F)	19:11	10:15
Age (years, SD)	13.1 (2.8)	12.9 (2.5)
Attention problems (SD) <sup>a</sup> .	54.2 (6.0)	59.4 (11.0)
Anxiety problems (SD)	53.2 (5.2)	56.2 (8.3)
IQ (SD)		90.4 (16.1)
Age at onset (years, SD, range)		7.3 (2.2)
Duration (years, SD)		3.9 (2.9)
None / Mono / Poly Therapy (N)		11 / 10 / 4
Epilepsy Seizure Type / Syndrome		
Generalized		8
Focal		6
Mixed		5
BECTS		5
CAE		1

<sup>a</sup>. Epilepsy patients had higher reported attention problems than healthy controls  $t$  ( $df = 36.2$ ) = 2.08,  $p = 0.045$ ,  $d = 0.59$ .

## **2.2. Dynamic Gaze Emotion Task**

Static colour images of 2 male and 2 female Caucasian models with five expressions of happy, sad, anger, fear and neutral<sup>27</sup> were modified to create a dynamic change from a neutral face with a direct gaze to a full expression with either a direct gaze or a simultaneous shift to averted gaze. This produced the four gaze and emotion conditions consistent with approach (happy and anger with direct gaze) and avoidance (fear and sad with averted gaze) motivations, in addition to a neutral condition. The stimuli subtended a visual angle of  $12^\circ \times 18^\circ$ , approximate to the dimensions of an average face viewed from a distance of 1 metre, and were 1200 ms in duration (see Figure 1). Full details on the production of the dynamic stimuli are described in the supplementary methods.

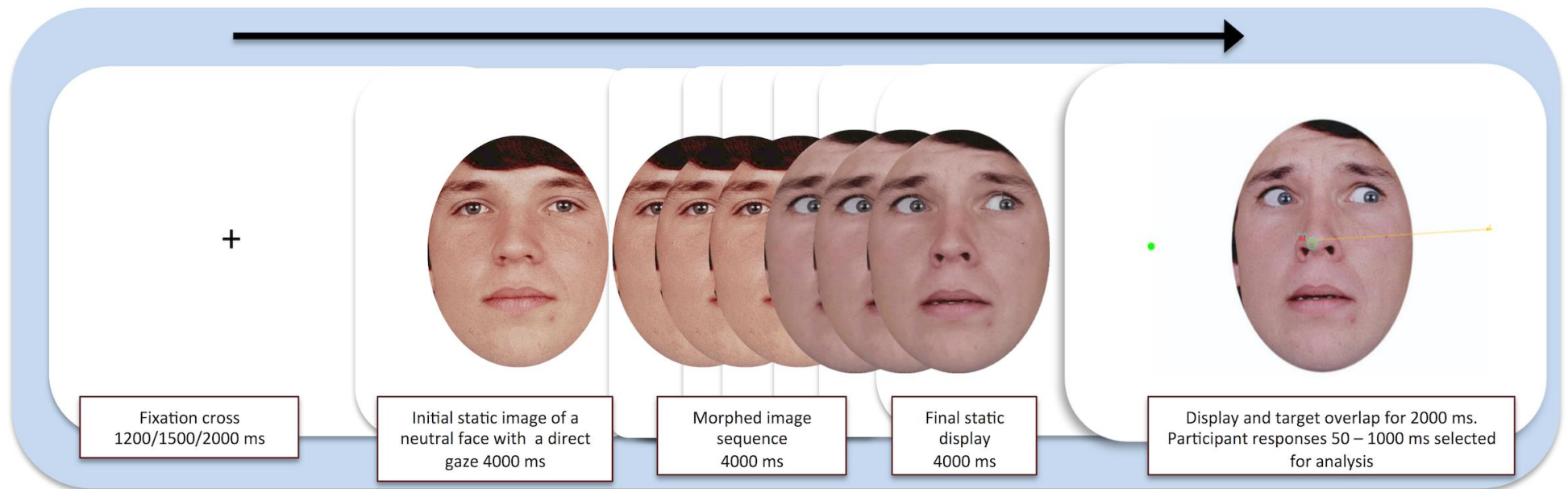


Figure 1. An example trial sequence of correct performance on an antisaccade incongruent gaze fear emotion trial

A fixation cross displayed for a variable duration followed by the dynamic stimuli for 1200 ms that consisted of an initial static display of a neutral face with direct gaze followed by the morphed sequence followed by the final static face display for the respective condition. Target presentation then overlapped with the final static image of the dynamic sequence and both the image and target remained on the screen for 2000 ms. The eye movement trace and recorded saccadic reaction time are also shown.

Emotion recognition of the four basic emotions (happy, anger, fear and sad) was assessed prior to the dynamic gaze and emotion experimental task. The test presented 16 static images (4 per emotion) with direct gaze in a randomized order for 1000 ms followed by the four emotion words (happy, sad, angry, fear) displayed until the child made a selection. The prosaccade (PS) and antisaccade (AS) dynamic emotion tasks each consisted of 120 trials (8 for each of the 15 conditions for the gaze and emotion combinations).

The PS and AS versions differed only in the instructions provided to the participants. Subsequent to a nine-point calibration procedure and a practice demonstration of correct performance children were provided with verbal instructions to fixate on a centrally presented fixation cross and told that dynamic images of emotional faces would be shown. Children were told that gaze direction was not predictive of target location and to respond as quickly as possible to the target that appeared after the dynamic images. On PS trials children were told to look quickly and accurately toward the target. On AS trials, children were told to inhibit a saccade toward the target and to look to the opposite side of the screen. A screen that displayed the eye-traces allowed the experimenter to monitor children's performance continuously and children were reminded of the task instructions after every 15 trials.

### **2.3. Eye Tracking Data**

Criteria for valid correct saccades were a first horizontal eye movement from the onset of the target in the direction consistent with task instruction, with a saccade reaction time (SRT) between 50 and 1000 ms and with an amplitude equal to or greater than 1° of visual angle. Further details of exclusionary criteria are reported in the supplementary methods. There was data loss one control on the AS task and a second control on the PS task (technical error). One patient was unable to complete the PS task as time constraints on the family meant terminating the session early.



## **2.4. Behavioural Problems**

The anxiety and the attention problems subscales from The Child Behavior Checklist (CBCL), 6-18 years was used in the study.<sup>28</sup> The scales are measured in T scores with a mean of 50 and SD of 10. A score above 65 is considered to identify clinical problems.

## **2.5. Ethics**

University and National Health Service ethics committees approved the study. Parents provided informed written consent and children informed assent prior to participation.

## **2.6. Statistical Analyses**

Analyses of the emotion recognition test found no group differences and outputs are in the supplementary information. There was 50% valid correct trials in the AS task compared to 80% of trials in the PS task, comparable to the proportion of valid correct AS previously seen in children.<sup>19</sup> The number of valid trials in the dynamic emotion task varied across individual children but no systematic differences existed between the groups or conditions. Two-level random intercept multilevel generalized linear mixed-effects models (GLMM) were therefore used to analyse the saccadic reaction times. An inverse Gaussian distribution and an identity link function were selected, appropriate for reaction time distributions.<sup>29</sup> The experiment included four different factors (Group, Instruction, Gaze Cue, Emotion) and a total of 30 conditions. Therefore analyses were hypothesis-driven as opposed to specifying full factorial models. First, to test for effects of Gaze Cue congruency a model was specified with the Instruction fixed effect with 2 levels (PS, AS), fixed effect of averted gaze cue with 2 levels (congruent cue, incongruent cue) and the interaction term (Instruction x Gaze Cue), and participant ID entered as a random effect with an intercept. This was conducted within the CWE and Controls groups for each of the discrete emotion conditions before entering the group fixed effect and interaction terms to compare groups, followed by tests of group differences for the direct gaze conditions. All pairwise group comparisons were Bonferroni adjusted. Age-related effects in atypical

performance were analysed by a split at the median age (younger: 8 – 12 years; older: 13-17 years) and assessing performance for younger and older patients and controls.

To explore predictors of atypical performance in the patient group, epilepsy-related variables, IQ and behavioural problems were entered in a systematic fashion and the best fitting model reported. Means and 95% Confidence Intervals [CIs] and p values are reported in the main body of the text. The statistical outputs of the GLMM models are in the supplementary information, with the exception of analyses of epilepsy and neurobehavioural factors that are tabulated below. All raw data are available at <https://dataverse.harvard.edu/dataverse/EMCWE>. All statistical analyses were performed in SPSS version 21.0 (IBM Corp., Armonk, NY).

### **3. Results**

#### **3.1. Averted Trials**

**3.1.1. CWE group:** The Instruction factor was significant for all five of the emotions conditions (all  $p < 0.001$ ) with slower AS than PS. The Gaze Cue main effect (congruent < incongruent) was significant in Happy ( $p = 0.04$ ), Sad ( $p = 0.005$ ) and Anger ( $p = 0.001$ ). It was non-significant for Fear ( $p = 0.11$ ) and Neutral ( $p = 0.10$ ). The Instruction x Gaze Cue interaction was significant in the Fear condition ( $p = 0.01$ ). Pairwise contrasts found a significant main effect of Gaze Cue in the PS task ( $p < 0.001$ ) that was absent in the AS task ( $p = 0.68$ ). The interaction term was non-significant in all other emotion conditions (all  $p \geq 0.46$ ). The estimated means (error bars = 95% CI) for Instruction and Gaze Cue for each emotion are presented in Figure 2a.

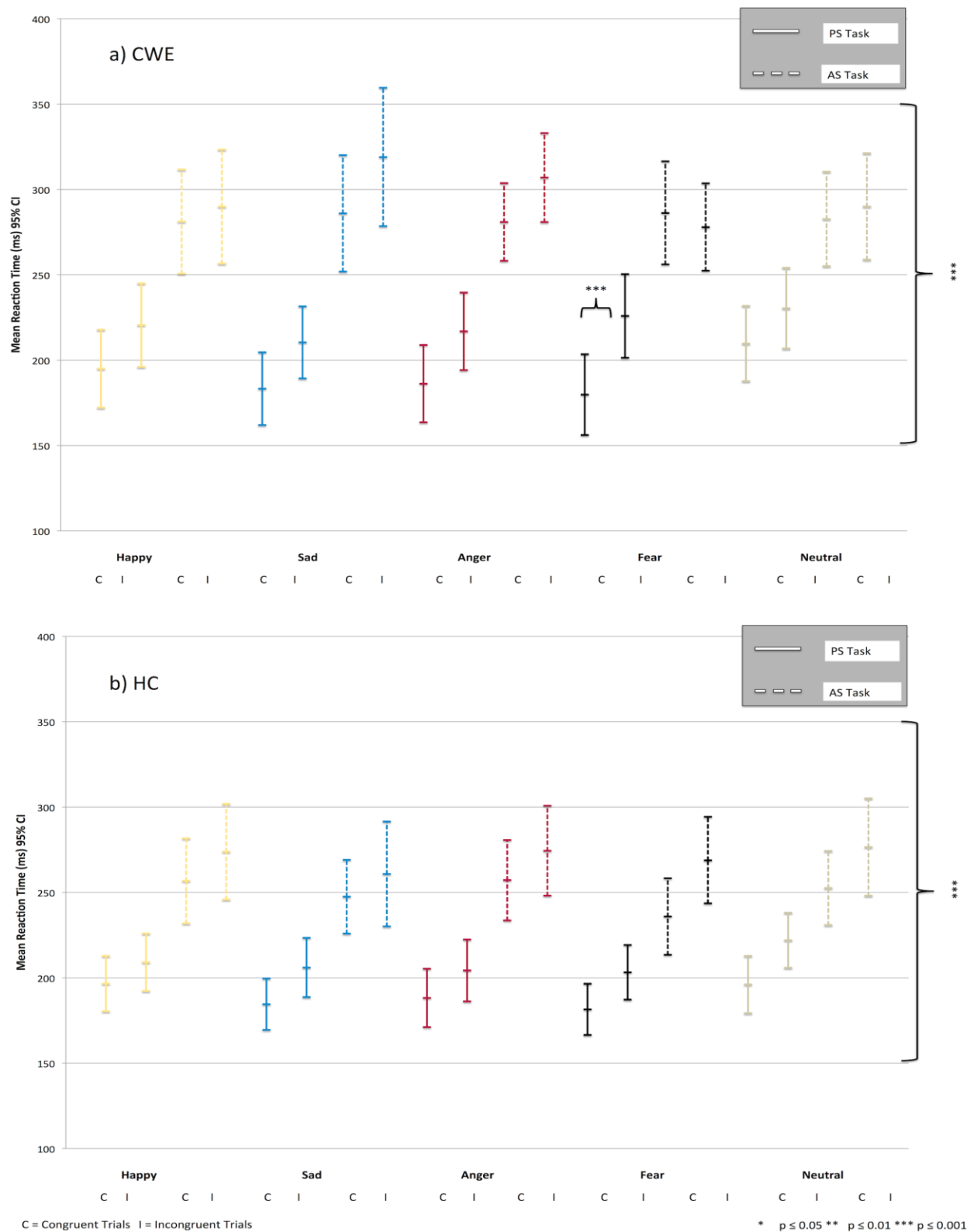


Figure 2a. Mean Reaction Times of Patients with Epilepsy in Antisaccade and Prosaccade Averted Gaze Trials Figure 2b. Mean Reaction Times of Healthy Controls in Antisaccade and Prosaccade Averted Gaze Trials.

**3.1.2. Control group:** Instruction was significant for all emotions conditions (all  $p < 0.001$ ) with AS slower than PS. Gaze Cue was significant in all emotion conditions: Happy ( $p = 0.02$ ) Sad ( $p = 0.01$ ), Anger ( $p = 0.01$ ), Fear ( $p = 0.001$ ) and Neutral ( $p < 0.001$ ). The Instruction x Gaze cue interaction term was non-significant in all emotion conditions (all  $p \geq 0.28$ ). The estimated means (error bars = 95% CI) for Instruction and Gaze Cue for each emotion are presented in Figure 2b.

**3.1.3. Group Comparisons:** There was no significant main effect of Group in Happy ( $p = 0.39$ ), Sad ( $p = 0.09$ ), Anger ( $p = 0.190$ ), Fear ( $p = 0.09$ ) or Neutral ( $p = 0.39$ ). There was an Instruction x Group interaction for Sad ( $p = 0.006$ ). CWE were slower than controls in the AS task ( $p = 0.018$ ) but not in the PS Task ( $p = 0.95$ ). The Instruction x Gaze Cue x Group interaction was significant in Fear ( $p = 0.007$ ). The pairwise contrasts showed that CWE were slower than Controls only on AS Congruent trials ( $p = 0.009$ ).

### **3.2. Direct Trials**

The main effect of Instruction was significant for all emotions conditions (all  $p < 0.001$ ) with AS slower than PS. The Group main effect was non-significant in all emotion conditions: Happy ( $p = 0.26$ ), Sad ( $p = 0.63$ ), Anger ( $p = 0.14$ ), Fear ( $p = 0.12$ ) and Neutral ( $p = 0.94$ ). There was a significant Instruction x Group interaction in Happy ( $p = 0.04$ ). Pairwise contrasts after adjustment found CWE tended to be slower than controls in the AS task ( $p = 0.07$ ) but did not differ from controls in the PS task ( $p = 0.64$ ). The Instruction x Group interaction was significant in Anger ( $p = 0.02$ ). CWE were slower than controls in the AS task ( $p = 0.04$ ) but not in the PS task ( $p = 0.82$ ). The interaction term was non-significant for all other emotion conditions (all  $p \geq 0.19$ ). The estimated means (error bars = 95% CI) of direct trials for CWE and controls are presented in Figure 3.

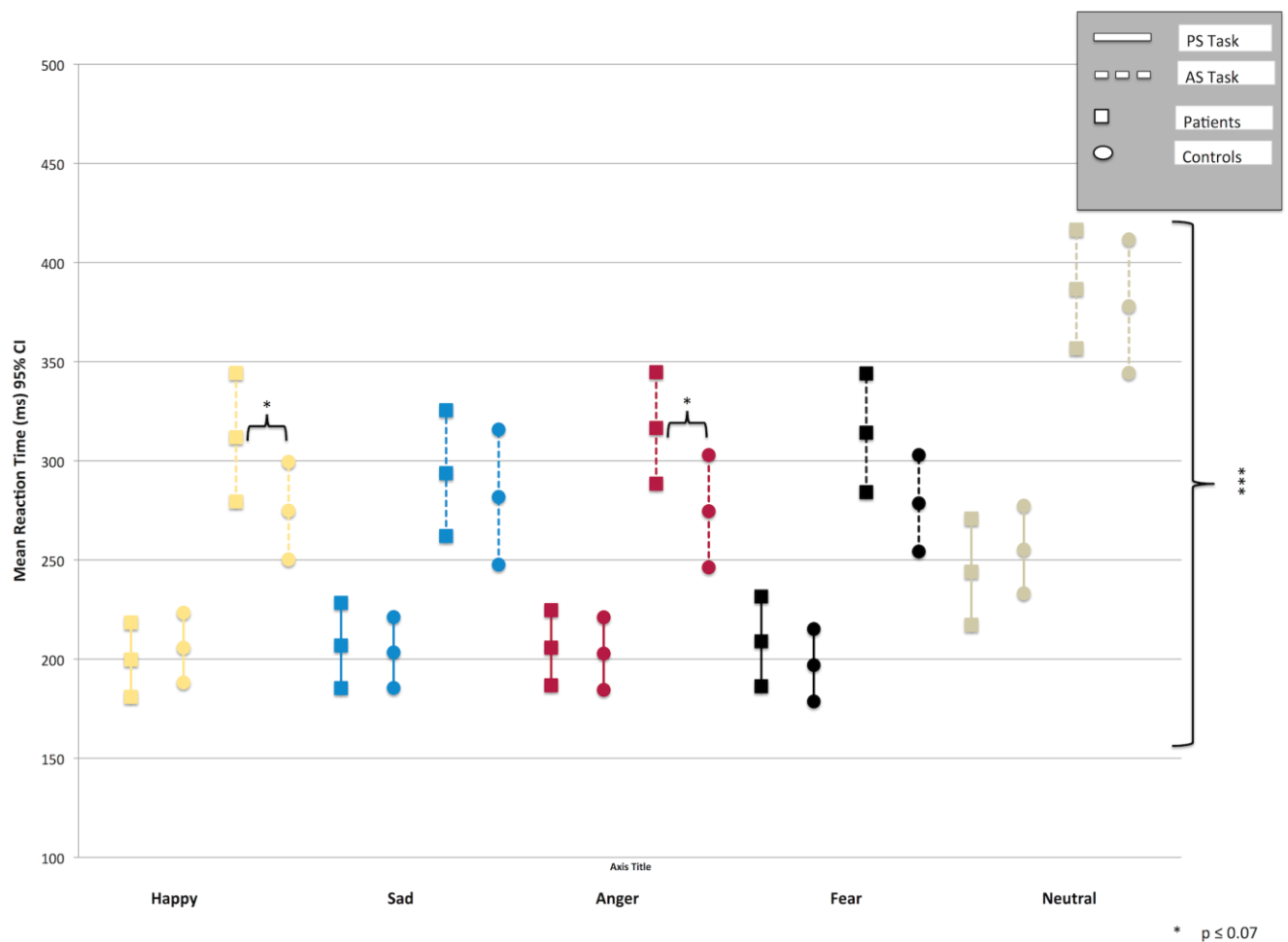


Figure 3. Mean Reaction Times of Patients and Controls in Antisaccade and Prosaccade Direct Gaze Trials

### 3.3. Age - related effects

**3.3.1. PS Task.** There was a Gaze Cue effect found in Fear in CWE. An analysis of Gaze Cue, Group and the interaction was performed in younger and older children.

**3.3.1.1 Younger children:** There was a significant main effect of Gaze Cue ( $p < 0.001$ ). No main group effect ( $p = 0.71$ ) and no interaction ( $p = 0.71$ ).

**3.3.1.2 Older children:** There was a significant main effect of Gaze Cue ( $p < 0.001$ ). No main group effect ( $p = 0.27$ ) whereas the interaction was significant ( $p = 0.005$ ). In

incongruent trials, older patients showed slower SRT  $M=237.5$  [198.7, 276.2] compared to older controls  $M= 187.8$  [160.2, 215.4].

**3.3.2. AS Task:** In the AS task, group differences were found in Fear and Sad averted trials, and Happy and Anger Direct trials.

**3.3.2.1 Younger children:** No differences between younger CWE and controls were found in AS Happy direct ( $p = 0.27$ ), Sad averted ( $p = 0.28$ ), AS Anger direct ( $p = 0.89$ ) or AS Fear averted ( $p = 0.63$ ). The Gaze Cue x Group Interaction found in Fear in the full group comparison was non-significant ( $p = 0.23$ ).

**3.3.2.2 Older children:** There were significant group differences found in Happy direct ( $p = 0.005$ ) Sad averted ( $p = 0.05$ ), Anger direct ( $p = 0.001$ ), and Fear averted ( $p = 0.005$ ). The Gaze Cue x Group interaction found in fear averted in the full group comparison was non-significant ( $p = 0.18$ ) as older CWE were slower than older controls on AS congruent trials ( $p = 0.001$ ) and AS incongruent trials ( $p = 0.06$ ). Performance on neutral trials was assessed as a control condition for emotion, no group differences were found in neutral averted (.25) or neutral direct conditions (.82). The estimated means (error bars = 95% CI) are presented in Figure 4.

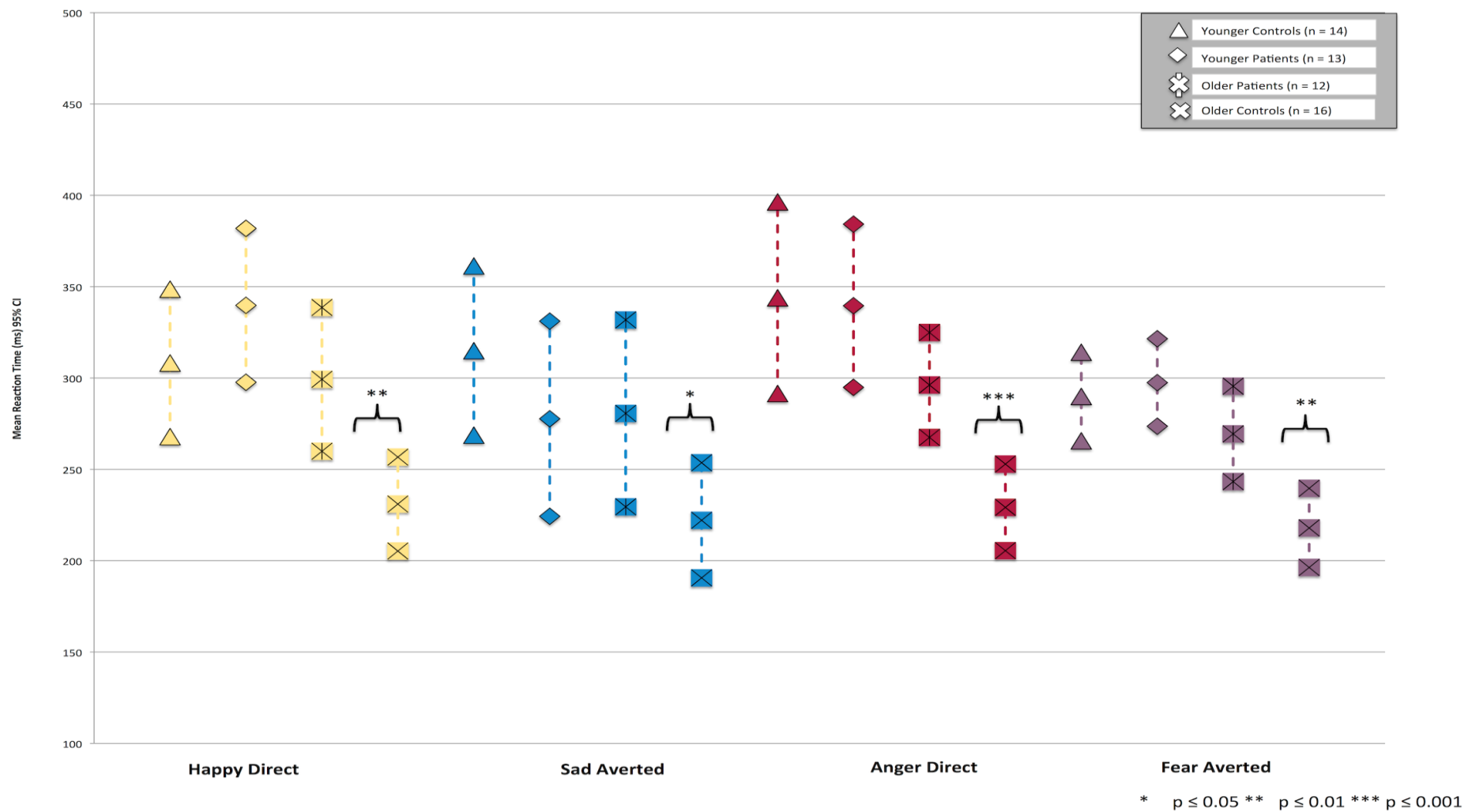


Figure 4. Mean Antisaccade Reaction Times of the Younger and Older Patients and Healthy Control Group

### **3.4. Epilepsy – related, cognitive and behavioural effects**

There were no significant differences between the younger and older patient groups in epilepsy-related variables, IQ or behavioural problems. Table 2 reports the results of the best fitting GLMM models on the SRT of PS and AS conditions where atypical performance was observed in patients.

**3.4.1. PS Task:** incongruent Fear Trials. Increased (slower) SRT was independently predicted by younger age, an older age at onset, a longer epilepsy duration, and higher anxiety scores. Note that no effects predicted responses to PS congruent fear trials.

**3.4.2. AS Task:** Happy Direct: Increased AS SRT was predicted by chronic epilepsy, an older age at epilepsy onset and higher anxiety. Sad Averted: Increased SRT was related to higher reported attention problems and a fixed effect of epilepsy type was also found. No pairwise comparisons survived adjustment however patients with a focal onset showed the slowest mean performance. Anger Direct: Slower SRT was predicted by greater attention problems (after controlling for the co-linearity with IQ). Fear Averted: Slower AS performance was significantly predicted by younger age or an older age at onset.



Table 2. Significant independent predictors of atypical saccadic reaction times (SRT) to dynamic gaze and emotions in children with epilepsy

	PS Fear Incongruent	AS Happy Direct	AS Sad Averted	AS Anger Direct	AS Fear Averted
Fixed Effects					
Gaze Cue					
Chronic epilepsy		F = 5.17, p = 0.04			
Epilepsy type			F = 14.85, p = 0.01		
Age	F = 6.42, p = 0.03				F = 20.28, p < 0.001
Age at Onset	F = 16.02, p = 0.02	F = 8.47, p = 0.05			F = 12.60, p < 0.001
Duration	F = 8.48, p = 0.02				
Anxiety	F = 10.05, p = 0.03	F = 4.35, p = 0.06			
Attention Problems			F = 11.97, p = 0.02	F = 5.40, p = 0.03	
IQ				F = 9.23, p = 0.02	
Random Effect					
Residual Variance	Z = 7.23, p < 0.001	Z = 5.88, p < 0.001	Z = 9.15, p < 0.001	Z = 6.32, p < 0.001	Z = 9.25, p < 0.001

#### 4. Discussion

This study assessed the modulatory effects of gaze and emotion cues on orienting to gaze under low and high cognitive control. Patient orienting to gaze cues was modulated by fear expressions under both low (prosaccade [PS]) and high (antisaccade [AS]) cognitive control, indicating a fear-related attentional bias that interfered with spatial orienting to gaze. Greater demand on control over attentional orienting led to slower processing of gaze and emotion expressions signalling motivational intent (shared signals) of both approach and avoidance. Independent of the contributory role of attention and anxiety problems, epilepsy developmental factors explained additional variance in response slowing. The pattern of findings suggests neurodevelopment of core social attention processes are vulnerable to adverse effects of epilepsy-related mechanisms, and play a contributory role in the most frequently reported neurobehavioural problems in childhood onset epilepsies.

The pattern of attentional orienting to averted gaze cues under PS and AS instructions were largely similar across patients and controls: both groups integrated gaze with task instruction, with faster orienting toward (pro) or away (anti) from gaze, similar to prior adult studies.<sup>18</sup> Fear signals modulated attentional orienting in patients and the slowed processing speed in incongruent PS and congruent AS trials is consistent with a delayed disengagement component of an attentional bias, as opposed to fear potentiated orienting towards threat.<sup>30</sup> The dynamic aspects of gaze and expressions are processed in a distributed network that includes the superior temporal sulcus (STS) and limbic structures<sup>31,32</sup> the intraparietal sulcus is also recruited for spatially directed attention in response to fear with averted gaze,<sup>33</sup> and this network shows increased functional integration with regulatory prefrontal networks across childhood to early adulthood.<sup>34</sup> In typical development, increased amygdala activity and decreased prefrontal activity is associated with response slowing to fear signals, with adolescence a period characterised

by asynchronous development of these subcortical and cortical systems.<sup>21</sup> Weakened prefrontal regulatory control over downstream affective reactivity in subcortical limbic structures is implicated in delayed disengagement from fear in paediatric anxiety.<sup>27</sup> Beyond evidence of age-related reductions in processing speed, delayed disengagement was also linked to increased epilepsy duration, pointing toward deleterious effects of continuing epileptiform activity on this cortical – subcortical functional integration. The amygdala is implicated in engagement and disengagement components of fear-related spatial orienting,<sup>35</sup> and it is important for future research to delineate amygdala hyperactivity versus weakened top-down control underlying this observed fear-related attentional bias in children with epilepsy.

The finding of longer latencies to shared signals in the AS task may be attributable to the slowed processing speed as a result of increased attentional control required for AS response preparation. Research with adults reports processing of shared signals are more likely to occur in individuals with slower response speeds,<sup>15</sup> an effect attributed to individual differences in gaze discrimination ability. Studies that manipulate the discriminability of gaze and expression report an overall processing speed advantage for judgements of gaze direction. However when discriminability of gaze is made more difficult, emotion expression is processed and gaze and emotion interactions are observed<sup>36</sup>. This suggests that in patients, top-down control compromised perceptual processing of gaze cues, and led to gaze and emotion expression interactions, reflecting possible underlying deficits in selective attention<sup>37</sup>. The findings also appear consistent with an affect-biased attentional mechanism<sup>38</sup>, whereby the effortful control needed for response preparation is accompanied by a susceptibility to perceptual filtering or tuning toward cues with motivational relevance.

No gaze and expression interactions emerged in the control group, consistent with studies in typical groups that used a simultaneous presentation of a gaze shift and expression, whereas <sup>13,39</sup> interactions are more frequently observed when the gaze shift occurs prior to expression (39). This suggests that in healthy controls, integration of emotion expression with gaze was not necessary to orient spatial attention under both low and high attentional control. An atypical developmental trajectory in social attention was clearly evident in patients, with similar average processing speeds observed in both younger and older patients, and group differences attributable to the typical maturational improvement in reaction times observed in healthy children.

The different pattern of predictors that emerged in the analyses of the discrete emotions can be understood within the context of protracted maturation of social perceptual processing across childhood and adolescence <sup>21</sup> and the increased salience of social motivational signals that characterises this developmental period.<sup>40</sup> Epilepsy developmental factors predicted response modulations to emotion displays associated with reward (happy) and threat-related (fear) signals, highly salient cues to motivational systems that undergo significant transformation during later childhood and adolescence.<sup>41</sup> The finding that onset in later childhood independently predicted slower processing speed replicates this same relationship with faster peak velocity of standard antisaccades we reported previously (42), implicating aberrant neurophysiological arousal mechanisms during increased cognitive control. Epilepsy onset in this period may also confer age-dependent vulnerabilities to emergent functional network connectivity that scaffolds the development of sophisticated social cognitive and affective processes, and behavioural regulation.

Examination of basic oculomotor, attentional and inhibitory functions was performed previously in this group of patients, using simple prosaccade and antisaccade tasks. <sup>42</sup> We found increased antisaccade latencies and impaired inhibitory control (increased errors) in

the medicated chronic patient subgroup, whereas an age-related improvement in inhibitory control was observed in CWE, independent of an effect of IQ.<sup>42</sup> In contrast, atypical performance on the social attention task could not be attributed only to the medicated subgroup, lower IQ, younger age, or behavioural problems. Furthermore, limited overall attentional resources in CWE would have resulted in increased reaction time variability, and no differential pattern of responding would have emerged. The finding of greater impairment in older patients is also inconsistent with the improved inhibitory control observed with older age in the non-social antisaccade task. Increased attention problems and greater anxiety also predicted those emotions where atypical responses are observed in respective neurodevelopmental and psychiatric populations. Notably, atypical processing of anger in attention disorders<sup>43</sup> and aberrant fear processes in anxiety,<sup>27</sup> indicate the social attention task probed deficits that are also shared with these comorbid conditions.

#### **4.1. Limitations**

Standard ophthalmic examination and assessment for neurodevelopment or psychiatric disorders was not implemented in the research program. The reported analyses only concerned correct performance. The size of the face stimuli was selected to reflect natural viewing conditions, the lack of a fixation cross however contributed to trial loss due to eye movements at target onset and it was difficult to classify errors as either reflexive saccades toward the sudden onset of the target or made in response to the gaze cue. The patient group was heterogeneous in terms of epilepsy and seizures types, the possibility of continuing seizures in the controlled epilepsy group could not be fully ruled out, and therefore analyses could only address effects that emerged despite this heterogeneity. This sample is consistent with children with epilepsy attending tertiary care. These are preliminary results that should be further explored in a larger population of patients.

#### **5. Conclusion**

Patients with epilepsy demonstrated relatively typical social orienting to gaze and basic emotion recognition but showed aberrant fear processing, particularly evident in patients with unremitting epilepsy. Greater demand on attentional control also appears to be associated with constrained flexibility in attentional allocation. Specifically, an extended perceptual processing of the social motivational relevance of gaze emotion cues was observed. Patients did not show a response pattern similar to younger healthy children, suggesting an atypical, as opposed to delayed, developmental trajectory. Epilepsy in childhood confers a risk to weakened attentional control over social perceptual processes that guide goal-directed actions, and contributes to adaptive social and affective development in adolescence. Epilepsy developmental and neurobehavioural factors represent different pathways to limitations on social attention, and this likely has implications for social adjustment and mental health in adulthood.

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## **References**

1. Hermann B, Seidenberg M, Jones J. The neurobehavioural comorbidities of epilepsy: can a natural history be developed? *Lancet Neurol.* 2008;7(2):151-60.
2. Itier RJ, Batty M. Neural bases of eye and gaze processing: the core of social cognition. *Neuroscience & Biobehavioral Reviews.* 2009;33(6):843-63.
3. Nummenmaa L, Calder AJ. Neural mechanisms of social attention. *Trends Cogn Sci.*

2009;13(3):135-43.

4. Monti G, Meletti S. Emotion recognition in temporal lobe epilepsy: a systematic review. *Neurosci Biobehav Rev*. 2015;55:280-93.

5. Taylor M, Mills T, Smith M, et al. Face processing in adolescents with and without epilepsy. *Int J Psychophysiol* 2008;68(2): 94-103.

6. Laurent, A., Arzimanoglou, A., Panagiotakaki, E., et al. 2014. Visual and auditory socio-cognitive perception in unilateral temporal lobe epilepsy in children and adolescents: a prospective controlled study. *Epileptic Disord*. 16 (4), 456–470.

7. Golouboff N, Fiori N, Delalande O et al. Impaired facial expression recognition in children with temporal lobe epilepsy: impact of early seizure onset on fear recognition. *Neuropsychologia*. 2008;46(5):1415-28.

8. Hermann B, Seidenberg M, Bell B, et al. The Neurodevelopmental Impact of Childhood- onset Temporal Lobe Epilepsy on Brain Structure and Function. *Epilepsia*. 2002 Sep 1;43(9):1062-71.

9. Lunn J, Lewis C, Sherlock C. Impaired performance on advanced Theory of Mind tasks in children with epilepsy is related to poor communication and increased attention problems. *Epilepsy Behav*. 2015;43:109-16.

10. Aaberg KM, Bakken IJ, Lossius MI, et al. Comorbidity and childhood epilepsy: a nationwide registry study. *Pediatrics*. 2016 Aug 1:e20160921.

11. Friesen CK, Kingstone A. The eyes have it! Reflexive orienting is triggered by nonpredictive gaze. *Psychon Bull Rev* 1998;5(3):490-5.

12. Frischen A, Bayliss AP, Tipper SP. Gaze cueing of attention: visual attention, social cognition, and individual differences. *Psychol Bull* 2007;133(4):694.

13. Neath K, Nilsen ES, Gittsovich K, et al. Attention orienting by gaze and facial expressions across development. *Emotion*. 2013;13(3):397.

14. Mathews A, Fox E, Yiend J, et al. The face of fear: Effects of eye gaze and emotion on visual attention. *Vis Cog.* 2003 Oct 1;10(7):823-35.
15. Adams Jr RB, Franklin Jr RG. Influence of emotional expression on the processing of gaze direction. *Motiv and Emot.* 2009;33(2):106-12.
16. Akechi H, Senju A, Kikuchi Y, et al. Does gaze direction modulate facial expression processing in children with autism spectrum disorder? *Child Dev.* 2009 Jul 1;80(4):1134-46.
17. Tottenham N, Hare TA, Casey B. Behavioral assessment of emotion discrimination, emotion regulation, and cognitive control in childhood, adolescence, and adulthood. *Front. Psychol.* 2011;2:39.
18. Wolohan FD, Crawford TJ. The anti-orienting phenomenon revisited: effects of gaze cues on antisaccade performance. *Exp Brain Res.* 2012;221(4):385-92.
19. Mueller SC, Hardin MG, Mogg K, et al. The influence of emotional stimuli on attention orienting and inhibitory control in pediatric anxiety. *J. Child Psychol. Psychiatry.* 2012;53(8):856-63.
20. Thomas LA, De Bellis MD, Graham R, et al. Development of emotional facial recognition in late childhood and adolescence. *Dev Sci.* 2007;10(5):547-58.
21. Hare TA, Tottenham N, Galvan A, et al. Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. *Biol Psychiatry.* 2008;63(10):927-34.
22. Scherf KS, Behrmann M, Dahl RE. Facing changes and changing faces in adolescence: A new model for investigating adolescent-specific interactions between pubertal, brain and behavioral development. *Dev Cogn Neurosci.* 2012;2(2):199-219.
23. Kellermann TS, Bonilha L, Lin JJ, et al. Mapping the landscape of cognitive development in children with epilepsy. *Cortex.* 2015;66:1-8.
24. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, Van Emde Boas W, et al.



- Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia*. 2010; 51(4):676–85.
25. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Allen Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*. 2010; 51(6):1069–77.
26. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014; 55(4):475–82.
27. Matsumoto D, Ekman P. Japanese and Caucasian Facial Expressions of Emotion (JACFEE) and Neutral Faces (JACNeuF). San Francisco: University of California, San Francisco. 1988.
28. Achenbach T, Rescorla L. Manual for the Achenbach system of empirically based assessment school-age forms profiles. Burlington, VT: Aseba. 2001.
29. Lo S, Andrews S. To transform or not to transform: using generalized linear mixed models to analyse reaction time data. *Front. Psychol*. 2015;6.
30. Cisler JM, Koster EH. Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. *Clin Psychology Review*. 2010 Mar 31;30(2):203-16.
31. Graham R, LaBar KS. Neurocognitive mechanisms of gaze-expression interactions in face processing and social attention. *Neuropsychologia*. 2012;50(5):553-66.
32. Haxby JV, Hoffman EA, Gobbini MI. The distributed human neural system for face perception. *Trends Cogn Sci*. 2000;4(6):223-33.
33. Hadjikhani N, Hoge R, Snyder J, et al. Pointing with the eyes: the role of gaze in communicating danger. *Brain Cogn* 2008;68(1):1-8.
34. Luna B, Garver KE, Urban TA, et al. Maturation of cognitive processes from late childhood to adulthood. *Child Dev*. 2004;75(5):1357-72.

35. Pishnamazi M, Tafakhori A, Loloee S, Modabbernia A, Aghamollaii V, Bahrami B, Winston JS. Attentional bias towards and away from fearful faces is modulated by developmental amygdala damage. *Cortex*. 2016 Aug 31;81:24-34.
36. Graham R, LaBar KS. Garner interference reveals dependencies between emotional expression and gaze in face perception. *Emotion*. 2007;7(2):296.
37. Ricciardelli P, Lugli L, Pellicano A, et al. Interactive effects between gaze direction and facial expression on attentional resources deployment: the task instruction and context matter. *Sci. Rep.* 2016;6.
38. Todd RM, Cunningham WA, Anderson AK, Thompson E. Affect-biased attention as emotion regulation. *Trends Cogn Sci*. 2012 Jul 31;16(7):365-72.
39. Lassalle A, Itier RJ. Emotional modulation of attention orienting by gaze varies with dynamic cue sequence. *Vis Cogn*. 2015;23(6):720-35.
40. Crone EA, Dahl RE. Understanding adolescence as a period of social– affective engagement and goal flexibility. *Nat Rev Neurosci*. 2012;13(9):636-50.
41. Spear LP. Adolescent neurodevelopment. *J Adolesc Health*. 2013;52(2):S7-S13.
42. Lunn J, Donovan T, Litchfield D, Lewis C, Davies R, Crawford T. Saccadic Eye Movement Abnormalities in Children with Epilepsy. *PloS one*. 2016 Aug 2;11(8):e0160508.
43. Köchel A, Leutgeb V, Schienle A. Disrupted Response Inhibition Toward Facial Anger Cues in Children With Attention-Deficit Hyperactivity Disorder (ADHD) An Event-Related Potential Study. *J Child neurol*. 2014;29(4):459-68.