Atypical novelty detection ERP responses associated with genetic but not idiopathic ASD etiologies

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Background

Attention in autism: Atypical attention and responsiveness to environmental changes are commonly reported among individuals with ASD [1,2] and may be related to downstream social communication impairments, repetitive behaviors, and circumscribed interests [2,3]. Numerous neural investigations of sensory processes subserving novelty detection have yielded mixed results. Neuroimaging studies suggest a reduced "alerting" response (e.g., dlPFC, STS/STG) towards novel stimuli, usually in a sequence of repetitive stimuli [21,22 23,24]. Similarly, studies using Oddball ERP paradigms have found a reduction in the the novelty detection P3a component in ASD[12,13,19,25-28]. However, findings of increased P3a response to novel stimuli have also been shown[16,18,29]. Although discrepant findings may be partially due to methodological differences across studies, heterogeneous genetic etiologies of ASD may be associated with divergent neural patterns of attention.

Genetic etiologies of autism: Recurrent disruptive likely gene disrupting (LGD) mutations such as *CHD8* and *DYRK1A* have been implicated as contributing to approximately 10% of ASD [30,31]. To better describe the known genetic and phenotypic heterogeneity in ASD, recent work has begun to target specific neural phenotypes related to specific genotypes. One such study integrating a "genetics-first" approach with cognitive neuroscience discovered unique social phenotypes related to genetic and idiopathic etiologies of ASD [32]. However, it is still unclear how genetic disruptions impact associated aspects of ASD such as atypical attention processes and contribute to phenotypic heterogeneity in ASD.

Objectives

Are inconsistent findings related to attention processes in ASD related to genetic etiology?

We sought to characterize the neural patterns associated novelty detection among children with idiopathic (i.e., no known genetic mutations) and genetic (i.e., truncated LGD mutation) ASD etiologies during a passive auditory oddball task.

Methods

- In an Oddball ERP paradigm, children watched a video of a trip to the zoo while passively attending to frequent tones (70%, e.g., 1000 Hz), infrequent tones (15%, e.g., 750 Hz), and novel sounds (15%, e.g., chime, creak).
- Maximum amplitude and peak latency at C_z , F_z , and P_z were extracted for the P3a component (180-350 ms). We focused on difference comparisons for novelty detection (novel vs. frequent).
- Mixed models were estimated for each region with full-factorial comparisons of Group, Condition, and Time in SAS 9.3. We statistically controlled for VIQ, NVIQ, age, and gender; none significantly contributed to models.

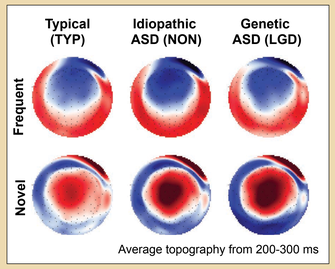
	Typically-developing (TYP)	Idiopathic ASD (NON)	Genetic ASD (LGD)
N	16	17	17
Male:Female	12:4	14:3	17:0
Age (SD)	13.3 (2.4)	13.3 (2.4)	13.7 (2.4)
VIQ (SD)	121.5 (37)	84.8 (41.5)	72.1 (29.6)
NVIQ (SD)	118.2 (35.7)	85.2 (39.4)	60.9 (22)
ADOS Total	N/A	7.5 (2.1)	8.2 (2.1)

LGD genes	
ARID1B	GRIN2B
CHD1	POGZ
CHD2 (x3)	SETD2
CHD8	TBR1
DSCAM	WDFY3 (x2)
DYRK1A (x2)	WDR33
FOXP1	

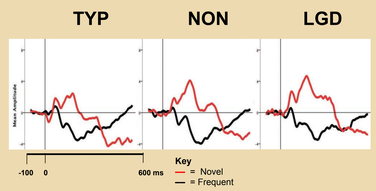
Results

P3a component (180-350 ms)

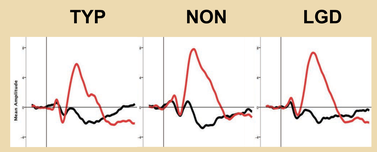
Topography of P3a



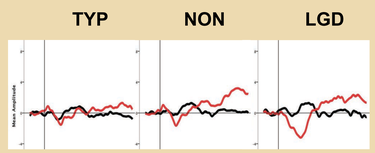
Waveforms at Fz



Waveforms at Cz



Waveforms at Pz

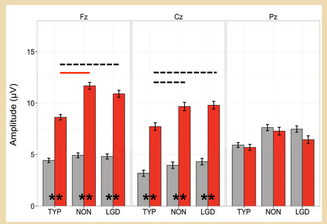


P3a Amplitude

All groups exhibited increased P3a for Novel sounds relative to Frequent tones at Cz and Fz. Both ASD groups exhibit a larger P3a response than TYP.

(1) ASD-NON:
- Larger P3a amplitude (2.26 μV at Cz; 2.93 μV at Fz) than TYP

(2) ASD-LGD:
- Marginally larger P3a amplitude (2.71 μV at Cz) than TYP



Significant Novel differences:
Fz: NON > TYP, $t(50.4)=2.44$, $p=.018$
Fz: LGD> TYP, $t(46.2)=1.72$, $p=.092$
Cz: NON > TYP, $t(54.3)=1.91$, $p=.061$
Cz: LGD > TYP, $t(54.3)=1.96$, $p=.055$

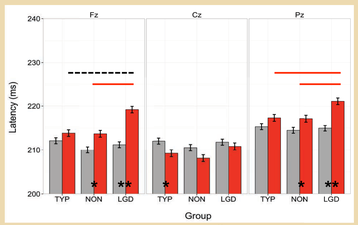
Key
* = condition discrimination, $p<.05$
** = condition discrimination, $p<.0001$
— = significant Novel group difference
- - = marginal Novel group difference

P3a Latency

Only TYP children had faster latencies for Novel sounds relative to Frequent tones at Cz.

(1) ASD-NON:
- Slower P3a latencies for Novel at Fz and Pz.

(2) ASD-LGD:
- Slower P3a latencies for Novel at Fz and Pz.
- Slower Novel compared to TYP (Pz) and NON (Fz, Pz).



Significant Novel differences:
Fz: LGD > TYP, $t(66.6)=1.90$, $p=.062$
Fz: LGD > NON, $t(97.5)=2.03$, $p=.045$
Pz: LGD > TYP, $t(84.3)=2.43$, $p=.017$
Pz: LGD > NON, $t(141)=2.07$, $p=.040$

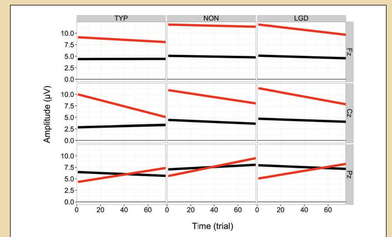
Key
* = condition discrimination, $p<.05$
** = condition discrimination, $p<.0001$
— = significant Novel group difference
- - = marginal Novel group difference

P3a Amplitude Dynamics

All regions exhibited change of amplitude over time (i.e. trial order).

(1) ASD-NON:
- Typical pattern of sensitization at Pz.

(2) ASD-LGD:
- Additional habituation at Fz.
- Typical pattern of habituation at Cz.
- Typical pattern of sensitization at Pz.



Significant ($p<.05$)	Fz	Cz	Pz
Novel (slope ≠ 0)	LGD*	TYP, NON*, LGD	TYP, NON, LGD
Frequent (slope ≠ 0)	--	--	--
Condition difference	--	LGD, TYP	TYP, NON, LGD

* marginal, $p<.1$; Habituation in blue; Sensitization in green

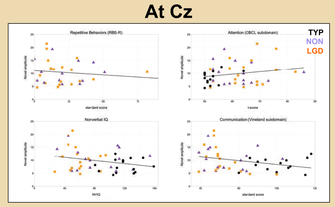
Correlation with Behaviors

Pearson correlations indicated larger Novel amplitudes correspond with:
- Less repetitive behaviors
- Less attention
- Lower NVIQ
- Lower communication

Domain (Measure)	Groups	Fz	Cz	Pz
Repetitive behaviors (ADOS composite)	ASD	**-0.043 (0.003)**	0.006 (0.708)	0.007 (0.634)
(RBS-R)	ASD	**-0.032 (0.036)**	**-0.041 (0.006)**	**-0.046 (0.002)**
Attention (CBCL)	TYP, ASD	0.019 (0.127)	**0.042 (0.001)**	**0.036 (0.004)**
Nonverbal IQ (DAS-II, Mullen)	TYP, ASD	**-0.045 (.0003)**	**-0.047 (.0001)**	-0.02 (0.096)
Communication (Vineland)	TYP, ASD	**-0.083 (<.0001)**	**-0.066 (<.0001)**	**-0.057 (<.0001)**

Note: *r* (*p*) values presented. Significant correlations are noted in BOLD.

At Cz



Discussion

Increased P3a in ASD

- Our findings supported prior work indicating an increased P3a novelty detection response [16, 18, 29], which may suggest a hypersensitivity to change in ASD.
- The ASD-LGD group showed a significantly longer P3a latency suggesting a divergent, and more impaired, pattern of novelty processing for children ASD and an associated *de novo* LGD mutation.

Considerations for habituation

- Importantly, the differences between ASD-NON and ASD-LGD may relate to differences in how attention resources are distributed over the course of the experiment.
- Future work assessing inter- and intra-hemispheric coherence may provide better insight regarding how ongoing processing is related to changes in functional connectivity.

Individual differences

- Our behavioral measures suggest that attention reductions may be strongly tied to other cognitive systems.
- Future work should investigate neural patterns of novelty detection among samples with greater recurrence of LGD mutations, and should continue to investigate how individual difference related to cognition and behavior relate to atypical attention processing abnormalities in ASD.

References
1. Allen, G. & Courchesne, E. *Frontiers in Bioscience-Landmark* 6, D105–D119 (2001).
2. Kasari, C., Mueller, R.-A. & Townsend, J. *Neuroscience & Biobehavioral Reviews* 37, 184–183 (2013).
3. Elsabbagh, M. *et al. J Child Psychol & Psychiat* 50, 240–252 (2013).
4. Clery, H. *et al. Psychophysiol* 50, 240–252 (2013).
5. Elsabbagh, M. *et al. J Child Psychol & Psychiat* 50, 642 (2009).
6. Zwaigenbaum, L. *et al. Int. J. Dev. Neurosci.* 23, 143–152 (2005).
7. Sen, S., Camguilm, A., Pisani, F. & Curatolo, P.*Clinical Neurophysiology* 110, 1825–1830 (1999).
8. Jansson-Verkasalo, E. *et al. Neuroscience Letters* 338, 197–200 (2003).
9. Kujala, T., Lepistö, T., Nieminen-von Wendt, T., Näätänen, P. & Näätänen, R. *Neuroscience & Biobehavioral Reviews* 29, 183–208 (2005).
10. Dunn, M. A., Gomes, H. & Gravel, *Journal of Autism and Developmental Disorders* 38, 52–71 (2008).
11. Kuhl, P. K., Coffey-Corina, S., Padden, D. & Dawson, G. *Developmental Science* 8, F1 (2005).
12. Lepistö, T. *et al. Brain Research* 1066, 147–157 (2005).
13. Lepistö, T. *et al. Clinical Neurophysiology* 117, 2161–2171 (2006).
14. Lepistö, T., Nieminen-von Wendt, T., Wendt, von, L., Näätänen, R. & Kujala, T. *Neuroscience Letters* 414, 136–140 (2007).
15. Korpilahti, P. *et al. Journal of Autism and Developmental Disorders* 37, 1539–1549 (2007).
16. Kujala, T. *et al. Biol Psychol* 75, 109–114 (2007).
17. Kujala, T. *et al. Clinical Neurophysiology* 121, 1410–1419 (2010).
18. Gomot, M. *et al. Journal of Autism and Developmental Disorders* 41, 705–714 (2011).
19. Kemner, C., Verbaten, M. N., Cuperus, J. M., Camfferman, G. & van Engeland, H. *Biological Psychiatry* 38, 150–165 (1995).
20. Ceponiene, R. *et al. Proceedings of the National Academy of Sciences* 100, 5567–5572 (2003).
21. Courchesne, O. & Lewa, A. *Reciprocal subcortical-cortical influences in autism: The role of attentional mechanisms.* (1999).
22. Gomot, M., Belmonte, M. K., Bullmore, E. T., Bernard, F. A. & Baron-Cohen, S. *Brain* 131, 2479–2488 (2008).
23. Keehn, B. & Joseph, R. M. *J Child Psychol Psychiatry* 49, 1296–1303 (2008).
24. Gold, M. S. & Gold, J. R. *Child Psychiatry Hum Dev* 6, 68–80 (1975).
25. Courchesne, E., Lincoln, A. J., Kilman, B. A. & Galambos, R. *Journal of Autism and Developmental Disorders* 15, 55–76 (1985).
26. Ferri, R. *et al. Clinical Neurophysiology* 114, 1671–1680 (2003).
27. Samson, C. H., Vargha-Khadem, F., Gadian, D. G., De Haan, M. & Baldeweg, T. *Clinical Neurophysiology* (2006).
28. Donkers, F. C. L. *et al. Journal of Autism and Developmental Disorders* 45, 506–523 (2013).
29. Gomot, M., Giard, M.-H., Adrien, J.-L., Barthélémy, C. & Bruneau, N. *Psychophysiol* 39, 577–584 (2002).
30. Iossifov, I. *et al. Nature* 515, 216–221 (2014).
31. Sanders, S. J. *et al. Neuron* 87, 1215–1233 (2015).
32. Hudac, C. M. *et al. Journal of Neurodevelopmental Disorders* 1–13 (2015). doi:10.1186/s11689-015-9118-5

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