Biological motion induced mu suppression is reduced in early Psychosis (EP) patients with active negative symptoms and autism spectrum disorders (ASD)

Minichino. Amedeo, Singh Fiza, Jaime Pineda, Elisabeth Friederich, Kristin S. Cadenhead

www.elsevier.com/locate/psychres

PII: S0165-1781(16)30145-7
DOI: http://dx.doi.org/10.1016/j.psychres.2016.01.057
Reference: PSY9417

To appear in: *Psychiatry Research*

Received date: 20 May 2015
Revised date: 24 November 2015
Accepted date: 26 January 2016

Cite this article as: Minichino. Amedeo, Singh Fiza, Jaime Pineda, Elisabetl Friederich and Kristin S. Cadenhead, Biological motion induced mu suppressio is reduced in early Psychosis (EP) patients with active negative symptoms an autism spectrum disorders (ASD), *Psychiatry Research* http://dx.doi.org/10.1016/j.psychres.2016.01.057

Biological Motion Induced Mu Suppression is reduced in Early Psychosis (EP) Patients with Active Negative Symptoms and Autism Spectrum Disorders (ASD).

Minichino Amedeo, MD[1,2]**, Singh Fiza,** MD[1]**, Jaime Pineda,** PhD[3]**, Elisabeth Friederich,** PhD[3]**, Kristin S. Cadenhead,** MD[1]

[1]Department of Psychiatry, University of California at San Diego (UCSD)

[2]Department of Neurology and Psychiatry, Sapienza University of Rome

[3]Department of Cognitive Science, Division of Cognitive Neuroscience, University of California at San Diego (UCSD)

Address Correspondence and Reprints to: Amedeo Minichino, M.D. Department of Psychiatry, 0810 University of California San Diego 9500 Gilman Drive La Jolla, CA 92093-0810 Phone: (415) 244-0441 Fax: (619) 543-7315 ; Email: amedeomin@gmail.com

Abstract

There is evidence of genetic and neural system overlap in ASD and EP. Five datasets were pooled to compare mu suppression index (MSI), a proxy of mirror neuron activity, in EP, high functioning ASD, and healthy subjects (HS). ASDs and EPs with "active" negative symptoms showed significant differences in mu suppression, in response to biological motion/point-light display animation, compared to HS. Preliminary findings suggest similar neural network deficits in ASD and EP patients with negative symptoms.

Key words: Mirror Neurons, posterior Superior Temporal Sulcus, Biological Motion

1. Introduction

Although ASD and SCZ are clinically distinct, evidence suggests genetic and neural systems overlap (King and Lord, 2011). Both spectra include negative symptoms as well as deficits in social-communicative skills, such as imitation, empathy, and joint attention (King and Lord, 2011). A dysfunction of the mirror neuron system (MNS) may be an underlying cause of these deficits (Burns, 2006). First discovered in the premotor area of the macaque monkey, putative MNS activity has also been demonstrated in humans involving circuitry of the inferior frontal gyrus, inferior parietal lobule, and posterior superior temporal sulcus (pSTS) (Burns, 2006).

While most studies investigating MNS activity in ASD indicate a hypofunctional system, in SCZ, MNS has been shown to be hyper-, hypo- or normal functioning (Mehta et al., 2014).

Mehta et al. propose a model in which the more persistent, trait-related, negative and social cognitive symptoms of SCZ may result from MNS hypofunction, while the phasic, state-related, positive and affective symptomatology could arise from a hyperfunction of the same system. In support of this theory, Singh et al (2011) reported that MNS hypoactivation was associated with negative symptoms and poor social functioning in EP individuals. This trait/state (hypo/hyper) model of the MNS functionality and the clinical heterogeneity of SCZ could explain the absence of relevant findings in some studies (Horan et al., 2014). Despite the growing number of studies investigating MNS in ASD and SCZ, none have directly compared these two spectra.

Given the above it is reasonable to expect that SCZ patients with negative symptoms, and thus, MNS hypofunction, would demonstrate MNS function profiles similar to ASD patients. To investigate this hypothesis, mu rhythm suppression (MS), an indirect index of MNS, was assessed in EP, high-functioning ASD and healthy subjects (HS). Disturbances in the detection of Biological Motion (BM) represented through point-light stimuli in both ASD and SCZ (Kim et al., 2011) is thought to result from aberrant activation of pSTS (Kim et al., 2011).

Data was pooled across 4 previously published (Pineda et al., 2008; 2014; 2011; Singh et al., 2011) and one unpublished (Friedrich et al., in preparation) studies to 1) Compare differences between EP, ASD and HS, and 2) the subset of EP patients with "active" negative symptoms (EP-N) versus those without negative symptoms (EP-NN). We hypothesized that MNS function would be reduced in both EP-N and ASD.

2. Methods

All studies used the same methodology and collected power in the 8–13 Hz ('mu') frequency band sampled over central electrodes (C3, C4 and Cz) during a baseline condition (the observation of a non-biological motion stimulus), during an observed hand action condition, a social interactive condition and a BM/point light display animation.

All EP subjects had an onset of psychotic symptoms within the last 2 years per the Structured Clinical Interview for DSM-IV. All ASD subjects were high functioning (IQ>80, evaluated using the Wechsler Adult Intelligence Scale, Third Edition). ASD diagnosis was based on the Autism Diagnostic Schedule and the Autism Diagnostic Interview, Revised.

To obtain comparably aged samples, only subjects >13 years, corresponding to the lower end of the EP sample, were included. The final sample included 20 EP (mean age: 19.1±4.3, 16 males), 16 ASD (15.0±1.3, 13 males) and 17 HS (19.7±6.5, 9 males).

Active negative symptoms in the EP group were defined as non-remitted symptomatology according to the Remission in Schizophrenia Working Group criteria (Andreasen et al., 2005).

Subgroups of EP patients with active negative symptoms (EP-N, n=15) or without negative symptoms (EP-NN, n=5) were selected for additional analyses.

Mu suppression was the ratio of mu power over central electrodes during action observation divided by mu power during the baseline condition.

3. Results

There were significant age differences between groups ($F(2,50)=6.78$, $p<0.05$), with EP and HS groups being older than ASD (p's<0.05). Pearson correlations between age and mu suppression were not significant across or within groups. The gender ratio did not differ between groups.

3.1 Biological Motion condition

Differences in MSI were tested by ANCOVA (covariate age) and post hoc t-tests and effect sizes - d (Figure 1). There was a significant group effect [$F(2,44)=4.98$, $p<0.01$]) that was accounted for by significant differences between ASD and HS ($p<0.01$, $d=1.11$) and EP and HS ($p<0.05$, $d=0.77$) . A four group analysis was performed with the EP group divided in EP-N and EP-NN. There was a significant group effect [($F(3,48)=3.08$, $p<0.05$)] (post-hoc: EP-N vs HS $p<0.01$, $d=0.84$; ASD vs HS $p<0.01$, $d=1.11$; ASD vs EP-NN $p=0.08$, $d=0.88$; EP-N vs EP-NN $p=0.25$, $d=0.71$).

3.2 Hand movement and Social Interactive condition

No significant group differences were found for these two conditions

Figure 1

4. Discussion

This is the first study comparing MNS in EP and ASD populations. Both groups showed deficits in MS, in response to BM animation, compared to HS. Within the EP group, those with active negative symptoms had the most prominent deficits.

In the case of ASD, patients are highly sensitive to non-social, physical contingencies and fail to recognize socially relevant biological motion, perhaps due to hypofunction of the pSTS (Shish et al., 2014). Some authors suggest that reduced pSTS function may be responsible for mentalization deficits, a core characteristic of ASD (Dichter, 2012). In contrast, studies investigating pSTS in SCZ show mixed results including no change, hyperactivation or

hypoactivation (Kim et al., 2011), consistent with the mixed MNS function results (Mehta et al., 2014).

Those findings have been reconciled through a theoretical framework where MNS function may be dependent on both "state" and "trait" factors in SCZ, but largely trait dependent in ASD. Positive symptoms may result from MNS hyperactivation, and may explain the tendency of psychotic subjects to mistakenly label actions and behaviors as having more intention than they actually have (Mehta et al., 2014). Negative symptoms and social cognitive deficits have been associated with reduced MNS function (Mehta et al., 2014). In line with this theory, in our study, EP patients with predominantly negative symptoms and ASD showed similar MNS hypofunction.

These preliminary findings suggest similar neural network deficits in ASD and a subset of EP patients with negative symptoms. One hypothesis to explain our results is that ASD arises earlier in neurodevelopment, and therefore, may represent a more stable dysfunction, whereas, EP which occurs later may represent a less fixed state.

4.1 Limits

Small sample size and age difference between the three groups. Not enough EP subjects with purely positive symptoms (N=2) to do subgroup analyses with this group.

REFERENCES

Andreasen, N.C., Carpenter, W.T. Jr, Kane, J.M., Lasser, R.A., Marder, S.R., Weinberger, D.R, 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. American Journal of Psychiatry 162(3):441-9.

Burns, J., 2006. The social brain hypothesis of schizophrenia. World Psychiatry 5(2):77-81.

Dichter, G.S., 2012. Functional magnetic resonance imaging of autism spectrum disorders. Dialogues in Clinical Neuroscience 14(3): 319–351.

Horan, W.P., Pineda, J.A., Wynn, J.K., Iacoboni, M., Green, M.F., 2014. Some markers of mirroring appear intact in schizophrenia: evidence from mu suppression. Cognitive, Affective, & Behavioral Neuroscience 14(3):1049-60.

Kim, J., Park, S., Blake, R., 2011. Perception of biological motion in schizophrenia and healthy individuals: a behavioral and FMRI study. PLoS One 6(5):e19971.

King. B.H., Lord, C., 2011. Is schizophrenia on the autism spectrum? Brain Research 22;1380:34-41.

Mehta, U.M., Thirthalli, J., Aneelraj, D., Jadhav, P., Gangadhar, B.N., Keshavan, M.S., 2014. Mirror neuron dysfunction in schizophrenia and its functional implications: a systematic review. Schizophrenia Research 160(1-3):9-19

Pineda, J.A., Brang, D., Hecht, E., Edwardsa, L., Careya, S., Bacona, M., Futagakia, C., Suka, D., Toma, J., Birnbauma, C., Rorka, A., 2008. Positive behavioral and electrophysiological changes following neurofeedback training in children with autism. Research in Autism Spectrum Disorders 2(3), 557–81.

Pineda, J. A., Pelton, H., Aragon, O., Bai, J-M, 2011. Behavioral and electrophysiological effects of induced neural plasticity in the autistic brain. In Valsamma Eapen (Ed), Autism: A Neurodevelopmental Journey from Genes to Behaviour, Nova Science Publishers.

Pineda, J.A., Carrasco, K., Datko, M., Pillen, S., Schalles, M., 2014. Neurofeedback training produces normalization in behavioural and electrophysiological measures of high- functioning autism. Philosophical Transactions of the Royal Society B: Biological Sciences 369(1644):20130183.

Shih, P., Keehn, B., Oram, J.K., Leyden, K.M., Keown, C.L., Müller, R.A., 2011. Functional differentiation of posterior superior temporal sulcus in autism: a functional connectivity magnetic resonance imaging study. Biological Psychiatry 70(3):270-7.

.

Highlights:

1)We pooled five previously published dataset to compare mu suppression index (MSI), a proxy of mirror neuron activity, in Early Psychosis individuals, high functioning Autism Spectrum Disorder (ASD) individuals, and healthy subjects (HS).

2)Both early psychosis and ASD individuals showed deficits in Mu Suppression, in response to a point/light Biological Motion animation, compared to HS.

3)Within the early psychosis group, those with active negative symptoms had the most prominent deficits.

4)To the best of our knowledge, this is the first study comparing mirror neuron system activity in patients with psychotic spectrum disorders and ASD.

Figure 1

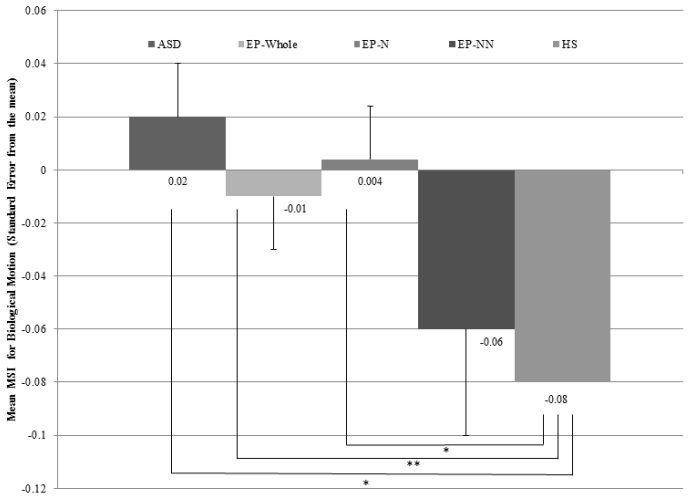

Figure 1. Comparison of average MSI mean for BM in ASD: Autism Spectrum Disorder, EP-Whole: Early Psychosis whole group, EP-N: EP with active negative symptoms, EP-NN: EP without active negative symptoms, HS: Healthy Subjects

*p<0.01, **p<0.05

Study	N. of subjects with age>13 (whole sample of the study)		Mean age (s.d.)	Gender: Male	
	ASD	HS			
Pineda et al., 2008	2 (19)	none		2 ASD	
Pineda et al., 2014	6 (19)	5 (16)		4 ASD	3 HS
Friedrich et al., 2015	6 (13)	none		5 ASD	
Pineda et al., 2011	2 (16)	none		2 ASD	
Total ASD	**16**		**15.0 (1.3)**	**13**	
	EP	HS			
Singh et al., 2011	20 (20)	12 (12)		16 FEP	6 HS
Total EP	**20**		**19.1 (4.3)**	**16**	
Total HS	**17**		**19.7 (6.5)**	**9**	

Table 1. Sample sizes, age and gender for studies included in this analysis. EP: Early Psychosis; ASD: Autism Spectrum Disorder; HS: Healthy Subjects.