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Singh, Fiza
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Biological Motion induced mu suppression is reduced in Early Psychosis (EP) patients with active negative symptoms and Autism Spectrum Disorders (ASD)

Amedeo Minichino [a,b,*], Fiza Singh [a], Jaime Pineda [c], Elisabeth Friederich [c], Kristin S. Cadenhead [a]

[a] Department of Psychiatry, University of California at San Diego (UCSD), San Diego, CA, USA
[b] Department of Neurology and Psychiatry, Sapienza University of Rome, Rome, Italy
[c] Department of Cognitive Science, University of California at San Diego (UCSD), San Diego, CA, USA

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ABSTRACT

There is evidence of genetic and neural system overlap in Autism Spectrum Disorder (ASD) and Early Psychosis (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 that similar neural network deficits in ASD and EP could be driven by the expression of negative symptoms in the latter group of patients. These findings may aid future studies on EP and ASD and facilitate the formulation of new hypotheses regarding their pathophysiology.

1. Introduction

Although Autism Spectrum Disorder (ASD) and Schizophrenia (SCZ) are clinically distinct, evidence suggests genetic and neural systems overlap (King and Lord, 2011). Both disorders 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 associated with these deficits (Williams et al., 2001; Burns, 2006). First discovered in the premotor area of the macaque monkey (di Pellegrino et al., 1992), 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) (Mukamel et al., 2010).

While most studies investigating MNS activity in ASD indicate a hypofunctional system (Williams et al., 2001; Buccino and Amore, 2008; Pineda et al., 2014), in SCZ, MNS has been shown to be hyper- (McCormick et al., 2012), hypo- (Singh et al., 2011; Mehta et al., 2014a; Mitra et al., 2014) or normal functioning (Horan et al., 2014). Mehta et al. (2014b) 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 Early Psychosis (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 has directly compared these two disorders.

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).

Data were pooled across 5 previously published (Pineda et al., 2008, 2014, 2011; Singh et al., 2011; Friedrich et al., 2015) studies to test the following hypotheses: 1) EP and ASD patients have an aberrant activation of the MNS compared to HS; 2) EP with "active" negative symptoms (EP-N) and ASD patients show similar MNS hypofunction.

* Correspondence to: Department of Psychiatry, 0810, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0810, USA.
E-mail address: amedeomin@gmail.com (A. Minichino).

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2. Methods

2.1. Subjects

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 (Table 1). Although two of the data sets utilized were collected as part of an intervention study (Pineda et al., 2008; Friedrich et al., 2015), the data used in the current analysis were collected prior to the intervention. 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) (more details are given in Table 1). The DSM-IV diagnoses in the EP group were the following: Schizophrenia ($n=1$), Schizophreniform disorder ($n=1$), Bipolar disorder with psychotic features ($n=1$) and Psychosis NOS ($n=17$).

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). A score > 2 in one of the four dimensions (Affective flattening, Avolition-apathy, Anhedonia-asociality, Alogia) of the Scale for Assessment of Negative symptoms (SANS) defined "active" negative symptomatology. 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.

Given the retrospective nature of the study, it was not possible to specifically evaluate negative symptom severity in the ASD group. Indeed, negative symptoms were not part of the clinical assessment of any of the ASD parent studies. However, a proxy measure of negative symptoms severity was obtained from the "sociability" subscale of the Autism Treatment Evaluation Checklist (ATEC, Geier et al., 2013). This subscale is composed of items, such as "poor eye contact", "avoids contact with others", "prefers to be left alone", "shows no affection", that explore similar constructs to those evaluated by the SANS. As previously shown by Singh et al. (2011), in our EP group negative symptoms burden, as measured by the SANS, correlated with Biological Motion (BM)-induced MNS activity. Starting from this observation, we evaluated if a proxy measure of negative symptoms, as measured by the score of the ATEC "sociability" subscale, could be related to BM-induced MNS activity in the ASD group as well.

2.2. Mu suppression procedure, EEG data acquisition and analysis

All studies used the same methodology. Data were collected while subjects watched videos of the following conditions: baseline/ball condition (Oberman et al., 2005), moving hand condition (Oberman et al., 2005), social interactive condition (Oberman et al., 2007) and a BM/point light display animation (Ulloa and Pineda, 2007). The movements in each video occurred at a frequency of 1 Hz and a continuous performance task was included to ensure that subjects were attentive to the stimulus. EEG data were collected from 5 electrodes applied directly to the scalp at the following locations: C3, Cz, C4, O1 and O2, using the international 10–20 method of electrode placement.

Data were collected for 80 s per condition at a sampling rate of 500 Hz. Eye and body movement related EEG segments, and any artifact activity were identified and eliminated prior to analysis. Data were segmented into epochs of 2 s beginning at the start of the segment. Data were only analyzed if there were at least 40 epochs available after rejection of artifacts. For each segment, integrated power in the 8–13 Hz range was computed using a Fast Fourier Transform performed on the epoched data (1024 points). A cosine window was used to control for artifacts resulting from data splicing. Mu suppression was calculated for central (C3, Cz and C4) and occipital (O1 and O2) sites using the equation: mu suppression = log 10 (mu power of experimental condition/mu power of ball condition) (Oberman et al., 2008). A log ratio less than zero indicates mu suppression, a log ratio equal to zero indicates lack of mu wave suppression and a log ratio greater than zero indicates mu enhancement.

A ratio was used to control for variability in absolute mu power as a result of individual differences such as scalp thickness and electrode impedance. Ratio data are inherently non-normal as a result of lower bounding, as such, we used a log transform for analysis.

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

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**	

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). Spearman correlations between age and mu suppression were not significant across or within groups. The gender ratio did not differ between groups ($X^2=2.75$, $p=0.25$).

3.1. Biological Motion (BM) condition

Differences in MSI were tested by analysis of covariance (ANCOVA, covariate age) and post-hoc t-tests and effect sizes – d (Fig. 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 ($n=20$) group divided into EP-N ($n=15$) and EP-NN ($n=5$). There was a significant group effect [($F(3, 48)=3.08$, $p < 0.05$)] that was accounted by significant differences between ASD and HS ($p < 0.01$, $d=1.11$), EP-N and HS ($p < 0.01$, $d=0.84$) and a marginally significant difference between ASD and EP-NN ($p=0.08$, $d=0.88$). The post-hoc analysis did not reveal any difference between EP-NN and HS ($p=0.58$, $d=0.12$) or between EP-N and ASD ($p=0.50$, $d=0.33$); EP-N and EP-NN did not significantly differ despite a medium effect size ($p=0.25$, $d=0.71$).

3.2. Hand movement and social interactive condition

No significant group differences were found for these two conditions

3.3. Correlation analysis between BM-induced MNS activity and the "sociability" subscale of the ATEC in the ASD group

In the ASD group, BM-induced MNS activity was significantly correlated with scores obtained in the "sociability" subscale of the

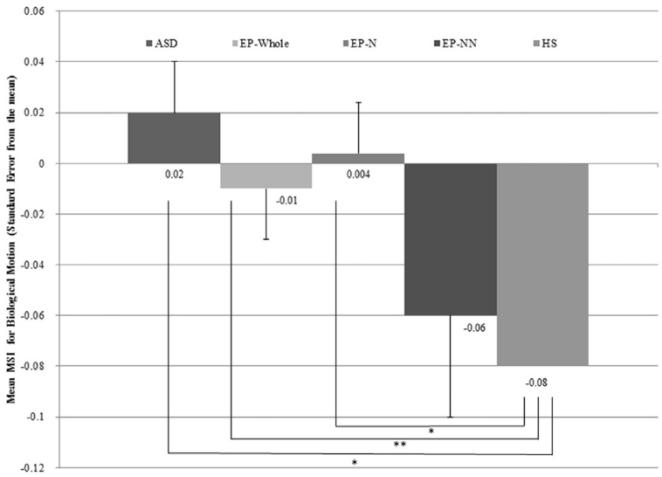

Fig. 1. Comparison of average MSI mean for BM in ASD: Autism Spectrum Disorder, EP-Whole: Early Psychosis whole group, EP-N: EP with active negative symptoms, EP-NN: EP without active negative symptoms, HS: Healthy Subjects $^{*}p < 0.01$, $^{**}p < 0.05$.

ATEC, such that subjects with greater symptoms severity showed lowest mu wave suppression (Spearman's rho=0.68 $p < 0.05$).

4. Discussion

This is the first study comparing MNS in EP and ASD populations. The first objective of the study was to the test the hypothesis that EP and ASD patients have an aberrant activation of the MNS compared to HS. Both EP and ASD individuals showed deficits in MNS, in response to BM animation, compared to HS. Disturbances in the detection of Biological Motion (BM) represented through point-light stimuli in ASD and SCZ (Kim et al., 2011; Singh et al., 2011) are thought to result from aberrant activation of pSTS (Kim et al., 2011).

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 (Shih et al., 2011). 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., 2014a).

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. In SCZ, 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., 2014b). Negative symptoms and social cognitive deficits have been associated with reduced MNS function (Mehta et al., 2014b). In line with this hypothesis and with the second objective of the study (i.e. to test the hypothesis that EP with "active" negative symptoms and ASD patients show a similar MNS hypofunction) the EP-N and ASD groups showed comparable MNS hypofunction. Furthermore, in ASD a proxy measure of negative symptoms significantly correlated with MNS hypofunction. This finding, even if preliminary given the small sample size and retrospective nature of the study, suggests that MNS hypofunction can be related to negative symptoms not only in EP individuals, as previously shown by Singh et al. (2011), but also to core stable tracts of the ASD condition, such as social withdrawal and isolation.

These preliminary findings suggest similar neural network deficits in ASD and a subset of EP patients with negative symptoms. One hypothesis to explain these 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. However, these findings need replication as they emerge from secondary analyses.

4.1. Limits

The main limitations of the study are the small sample size and the age difference between the three groups. Other limitations are: (i) the small sample of the EP-NN group ($n=5$), too small for any fair statistical analysis and (ii) the lack of enough EP subjects with purely positive symptoms ($N=2$) to do subgroup analyses with this group.

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