

# Differential Patterns of Visual Sensory Alteration Underlying Face Emotion Recognition Impairment and Motion Perception Deficits in Schizophrenia and Autism Spectrum Disorder

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## ABSTRACT

**BACKGROUND:** Impaired face emotion recognition (FER) and abnormal motion processing are core features in schizophrenia (SZ) and autism spectrum disorder (ASD) that have been linked to atypical activity within the visual cortex. Despite overlaps, only a few studies have directly explored convergent versus divergent neural mechanisms of altered visual processing in ASD and SZ. We employed a multimodal imaging approach to evaluate FER and motion perception in relation to functioning of subcortical and cortical visual regions.

**METHODS:** Subjects were 20 high-functioning adults with ASD, 19 patients with SZ, and 17 control participants. Behavioral measures of coherent motion sensitivity and FER along with electrophysiological and functional magnetic resonance imaging measures of visual pattern and motion processing were obtained. Resting-state functional magnetic resonance imaging was used to assess the relationship between corticocortical and thalamocortical connectivity and atypical visual processing.

**RESULTS:** SZ and ASD participants had intercorrelated deficits in FER and motion sensitivity. In both groups, reduced motion sensitivity was associated with reduced functional magnetic resonance imaging activation in the occipitotemporal cortex and lower delta-band electroencephalogram power. In ASD, FER deficits correlated with hyperactivation of dorsal stream regions and increased evoked theta power. Activation of the pulvinar correlated with abnormal alpha-band modulation in SZ and ASD with under- and overmodulation, respectively, predicting increased clinical symptoms in both groups.

**CONCLUSIONS:** SZ and ASD participants showed equivalent deficits in FER and motion sensitivity but markedly different profiles of physiological dysfunction. The specific pattern of deficits observed in each group may help guide development of treatments designed to downregulate versus upregulate visual processing within the respective clinical groups.

**Keywords:** Autism, EEG, FER, Motion, Schizophrenia, Visual

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The ability to rapidly and accurately perceive and respond to facial expressions is an important component of social functioning. Impaired face emotion recognition (FER) in schizophrenia (SZ) (1–3) and autism spectrum disorder (ASD) (4–8) correlates significantly with symptoms (9) and functional outcome (10,11). Visual motion perception facilitates the detection of facial and bodily cues important for socioemotional communication (12). Motion discrimination is impaired in both SZ [reviewed in Chen (13)] and ASD (14–16). Despite their shared characteristics, the neural mechanisms underlying FER and motion deficits in SZ and ASD are poorly understood.

Processing complex visual stimuli depends on coordinated functioning of cortical/subcortical components of the visual

system. These include early, ventral, and dorsal regions [reviewed in Fusar-Poli *et al.* (17) and Glasser *et al.* (18)] as well as subcortical structures such as the pulvinar nucleus of the thalamus (19,20). Together, these regions contribute to analysis of features of the visual environment and coordination of activity across visuocortical areas. Abnormal neural responses of these cortical regions and the pulvinar have been reported in SZ (21–24) and ASD (25–28) and may contribute to impairments in both FER and motion perception.

Here, we used electrophysiological and functional neuroimaging approaches to investigate convergent and divergent patterns of visual processing in SZ and ASD in relation to FER. Electrophysiological responses have high temporal but low

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spatial resolution and are well suited to analysis of brain activity at the ensemble level (29). By contrast, neuroimaging methods such as task-based and resting-state functional magnetic resonance imaging (fMRI) have high spatial resolution and are particularly suitable for evaluating subcortical and corticocortical connectivity patterns.

Electrophysiological responses to stimulus onset, motion onset, and oscillatory entrainment were obtained and analyzed in the frequency domain to differentiate processing-specific patterns of neural activity. Activity associated with stimulus processing occurs primarily in the theta (4–7 Hz) frequency band (30), whereas activity associated with processing stimulus motion occurs primarily at delta (1–4 Hz) frequencies (31). In both cases, these responses are tightly phase locked to stimulus and motion onset, respectively, thus leading to increases in evoked power. The appearance of visual stimuli additionally induces a reduction of ongoing alpha (7–14 Hz) activity (event-related desynchronization [ERD]) over the occipital cortex, believed to occur when cortical regions are brought “on-line” for information processing (32,33). The alpha ERD response is not phase locked to the eliciting stimulus, and therefore changes in oscillatory power are analyzed using single-trial analysis.

fMRI was used to localize disturbances within subcortical and cortical visual regions during motion processing, and resting-state fMRI was used to evaluate connectivity between these regions. Aberrant connectivity, including thalamocortical connectivity, has been reported previously in both SZ (34,35) and ASD (36,37), but the association between these disrupted circuits and impaired visual processing has not been investigated.

Based on prior studies, we hypothesized that SZ and ASD participants would have convergent deficits in FER and motion processing, consistent with convergent disturbances in social cognition. We also hypothesized that participants would show intercorrelated disturbances in electrophysiologic and fMRI-based measures related to behavioral performance. The present study evaluates the degree to which neural mechanisms underlying these disturbances are convergent or divergent across disorders.

## METHODS AND MATERIALS

### Participants

Participants were 19 patients with SZ, 20 individuals with ASD, and 17 control subjects (CNs), recruited from the central database at the Nathan Kline Institute for Psychiatric Research. All were without significant medical/neurological disorders. SZ diagnoses (determined <1 year from participation) used the Structured Clinical Interview for DSM-IV (38). Symptoms were evaluated using the Positive and Negative Syndrome Scale (39) (<3 months from participation). All SZ patients were on a stable dose of antipsychotic medication. ASD diagnoses were determined by DSM criteria and confirmed by the Autism Diagnostic Observation Schedule, Second Edition (<3 months from participation). Any participant meeting diagnostic criteria for both SZ and ASD or with IQ <70 was excluded. IQ [Ammons Quick Test (40)] and education levels were lower in SZ patients compared with CNs (Supplemental Table S1). All participants had minimum 20/22

corrected visual acuity on a Logarithmic Visual Acuity Chart. The investigation was approved by the Nathan Kline Institute for Psychiatric Research Institutional Review Board. Informed consent was obtained after all procedures had been fully explained. The study was carried out in 2 experimental sessions (scheduled <4 weeks apart).

### Behavioral Measures

**Coherent Motion Detection.** Coherent motion thresholds were determined using random-dot kinematograms (Supplemental Figure S1A). Coherence thresholds at 82% correct were determined by the QUEST (Quick Estimation) procedure (41) from 100 trials. Motion sensitivity scores were defined as 1/coherence threshold. Data from 1 ASD participant were unavailable.

**Face Emotion Recognition.** FER was evaluated using the Penn Emotion Recognition Task (42,43). Scores were unavailable from 2 CNs and 1 ASD participant.

### Electrophysiology

**Stimuli and Task.** The present study utilizes a previously described paradigm (31) (Supplemental Figure S1B). Stimuli were grayscale sinusoidal gratings of low spatial frequency (0.8 cpd) at high (75%) or low (8%) luminance contrast or high spatial frequency (5 cpd) at high luminance contrast. On each trial, stimuli appeared (400 ms), drifted rightward (200 ms), then counterphase-reversed at 10 Hz (3000 ms), yielding a steady-state visual evoked potential (ssVEP). Participants responded by button-press to occasional dimming of a central fixation cross.

**Recordings and Data Analysis.** The electroencephalogram (EEG) was recorded using a waveguard cap (ANT Neuro, Enschede, Netherlands) containing 64 equally spaced electrodes (44) with a sampling rate of 512 Hz and re-referenced offline to the average of all electrodes. Blink-related artifacts were removed by independent component analysis. Epochs with amplitudes exceeding  $\pm 100 \mu\text{V}$  at any electrode were excluded. On average, 7.2% (CNs), 12.8% (patients with SZ), and 9.1% (ASD participants) of trials were excluded. Analyses were performed using MATLAB (version R2015b; The MathWorks, Inc., Natick, MA) with the EEGLAB and ERPLAB toolboxes (45).

**Evoked Power Analyses.** Event-related activity was analyzed separately for each stimulus type. Evoked-power measures were obtained by convolving the time domain-averaged event-related potentials (time locked to stimulus onset) with a 3-cycle Morlet wavelet over a 3-second window, beginning 1 second before onset, as described previously (31). Evoked power was extracted at each time point over 74 frequency scales (0.48–27.6 Hz), incremented logarithmically. Statistical analyses were carried out in theta (4–7 Hz) and delta (1–4 Hz) frequency bands, for stimulus-onset and motion-onset activity, respectively. Measurement latency windows were centered around the peak amplitude based on combined data from all participants, yielding a theta window of 150 to

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250 ms poststimulus onset and a delta-window of 50 to 250 ms postmotion onset.

**ssVEP Analyses.** ssVEP data were analyzed at the driving stimulation frequency (10 Hz) using fast Fourier transform and tested between 500 and 3000 ms following the onset of counterphase stimulation.

**Single-Trial Power Analyses.** The single-trial EEG signal from each channel was convolved with a 3-cycle Morlet wavelet, and total power was extracted as above. The alpha ERD was measured as the reduction in total power within the alpha (7–14 Hz) frequency, from the prestimulus (–150 to 0 ms) to poststimulus latency interval, and tested between 250 and 400 ms poststimulus onset.

### Functional MRI

**Stimuli and Task.** Motion-sensitive visual areas were identified using low-contrast concentric rings (15 degrees diameter) extending throughout a circular region (31,46). Participants monitored a central cross and responded via button-press to occasional dimmings. The rings expanded/contracted for 20 seconds followed by 20 seconds during which the stimuli were static (Supplemental Figure S1C).

**Acquisition and Data Analysis.** Functional images were acquired on a Siemens 3T TIM-Trio scanner (Siemens Corp., Erlangen, Germany). Preprocessing included despiking, slice time, and motion correction. Anatomical surfaces were generated from high-resolution images using FreeSurfer (47), registered to the 141-fsaverage standard mesh. Post-processing and statistical analyses were carried out on gray-matter ordinates of the surface using a combination of AFNI (48) and SUMA (<https://afni.nimh.nih.gov/Suma>) software. Single-participant analyses of the contrast of moving versus stationary stimuli used general linear model procedures incorporated in AFNI. The HCP-MMP1.0 cortical parcellation (18), registered to the FreeSurfer standard mesh, was used to extract beta parameters from the V1, early visual, dorsal, ventral, and middle temporal complex (MTC) regions (18) of the left and right hemispheres. Beta values were also extracted from the pulvinar nucleus [individually parcelled using FreeSurfer (49)], following parallel processing/general linear model procedures of volumetric data. Group-wise analyses were carried out on mean beta values from these 6 regions. Significance levels were set to a (corrected)  $p < .01$ .

**Resting-State Functional Connectivity.** Resting-state images (180 acquisitions) were acquired during one 6-minute scan and preprocessed as above. Additional preprocessing on the surface was performed to remove physiological confounds and 24 motion parameters. Average signal time-courses were extracted from each cortical/subcortical region and pairwise correlated.

### Random Forest

The random forest (RF) machine learning method (50) was used to test the ability of electrophysiological and fMRI measures of brain function for discriminating 1) between ASD and

SZ and 2) among all 3 groups, at an individual level. In both analyses, the number of trees was set to 5000 and 3 variables were tried at each tree node split. The R package randomForest (51) was used for analyses (version 3.4.1; The R Foundation for Statistical Computing, <http://www.R-project.org>). Generalization error was based on classification accuracy of out-of-bag samples.

### Statistics

Between-group comparisons used 1-way or repeated-measures analysis of variance. For EEG analyses, factors were stimulus type (low-contrast low spatial frequency, high-contrast low spatial frequency, high-contrast high spatial frequency) and (where appropriate) hemisphere (left, right). Tukey honestly significant difference tests were used for post hoc comparisons.

Analyses of covariance assessed the interrelationship between physiological (EEG/fMRI, covariates) and behavioral (FER/motion sensitivity) measures with group membership as a categorical predictor. The group  $\times$  covariate interaction assessed homogeneity of slopes. Analyses of covariance were followed by within-group Pearson correlation or stepwise regression. Correlations were considered significant after Bonferroni-corrected  $p$  values for the number of tests.

## RESULTS

The effects of gender and age were analyzed by multivariate analysis of variance using the means from all physiological/behavioral variables. The main effect of gender ( $F_{1,47} = 0.207$ ,  $p = .651$ ), and the group  $\times$  gender ( $F_{2,47} = 1.72$ ,  $p = .191$ ) and the variable  $\times$  gender ( $F_{13,35} = 1.82$ ,  $p = .085$ ) interactions were nonsignificant; thus, subsequent analyses collapsed across gender.

Across groups, there was a main effect of age ( $F_{2,53} = 3.96$ ,  $p = .025$ ), with no age differences between patients with SZ ( $F_{1,34} = 0.947$ ,  $p = .337$ ) and ASD participants ( $F_{1,35} = 3.02$ ,  $p = .091$ ) compared with CNs. When regressed against age, none of the physiological measures were significantly associated with age ( $p < .250$ , all). Unless noted, subsequent analyses did not include age as a factor.

### Motion and Face Emotion Processing, Behavioral Measures

FER (Penn Emotion Recognition Task scores) ( $F_{2,48} = 6.99$ ,  $p = .002$ ) and motion sensitivity ( $F_{2,50} = 9.37$ ,  $p < .001$ ) differed significantly across groups even following control for age and IQ. This difference also remained significant after excluding participants ( $n = 10$ ) with motion sensitivity scores  $< 4$  ( $F_{2,39} = 5.54$ ,  $p = .007$ ).

Compared with CNs, FER was significantly reduced in patients with SZ ( $F_{1,32} = 23.61$ ,  $p < .001$ ) and ASD participants ( $F_{1,32} = 11.20$ ,  $p = .002$ ), as was motion sensitivity (SZ [ $F_{1,34} = 19.47$ ,  $p < .001$ ] and ASD [ $F_{1,34} = 9.07$ ,  $p = .005$ ]) (Supplemental Figure S2A).

Motion sensitivity predicted FER across groups ( $F_{1,47} = 9.47$ ,  $p = .003$ ) but the relationship differed significantly, as reflected in a group  $\times$  motion sensitivity interaction ( $F_{2,47} = 7.73$ ,  $p = .001$ ). Within groups, FER correlated with motion sensitivity in CNs ( $r = .542$ ,  $p = .037$ ) and ASD subjects

( $r = .570, p = .011$ ) as well as across both groups ( $r = .661, p < .001$ ). In SZ, the correlation was not significant ( $r = -.357, p = .133$ ) (Supplemental Figure S2B).

### Electrophysiological Results

Behaviorally, correct target detections ( $F_{2,53} = 1.80, p = .176$ ) and false alarm rates ( $F_{2,53} = 2.65, p = .080$ ) did not differ significantly across all groups but were lower in patients with SZ compared with CNs (Supplemental Table S1).

**Stimulus Onset Response (Theta).** Stimulus onset elicited an increase in evoked theta power, which differed significantly across groups ( $F_{2,53} = 10.27, p < .001$ ) (Table 1). Relative to CNs, mean theta power was reduced in patients with SZ ( $p = .009$ ) but was increased in ASD subjects ( $p = .038$ ) (Figure 1B).

Across groups, mean theta power significantly predicted FER ( $F_{1,47} = 7.38, p = .009$ ). The group  $\times$  theta interaction ( $F_{2,47} = 7.97, p = .001$ ) was also significant. In follow-up correlations, enhanced theta activity in ASD subjects correlated with reduced FER ( $r = -.722, p < .001$ ) (Figure 1C). This correlation was not significant within the SZ or CN groups ( $p > .500$ ). Finally, theta power was not a significant predictor of motion sensitivity ( $F_{1,49} = 1.86, p = .179$ ).

**Motion Onset Response (Delta).** Motion onset elicited an increase in delta (1–4 Hz) evoked power, which differed across groups ( $F_{2,53} = 6.20, p = .004$ ), with significant reductions in both patients with SZ ( $p = .020$ ) and ASD participants ( $p = .007$ ) compared with CNs (Figure 1D).

Mean delta power did not predict FER scores ( $F_{1,47} = 0.333, p = .566$ ) but did predict motion sensitivity ( $F_{1,49} = 5.96, p = .018$ ) across groups, with a significant difference in the slopes of the effect (group  $\times$  delta interaction [ $F_{2,49} = 4.51, p = .007$ ]). Reduced delta power in patients with SZ ( $r = .461, p = .047$ ) and ASD subjects ( $r = .598, p = .007$ ) correlated with lower motion sensitivity (Figure 1E).

**Alpha Measures.** Alpha ERD amplitude differed significantly across groups ( $F_{2,53} = 8.91, p = .0005$ ) (Figure 2A, B; Table 1) and was reduced in patients with SZ compared with both CNs ( $p = .017$ ) and ASD subjects ( $p < .001$ ) (Figure 2B). In ASD subjects, ERD amplitude was larger ( $p = .039$ ) and temporally prolonged ( $p = .021$ ) relative to CNs. Across groups, alpha ERD predicted neither FER ( $F_{1,47} = 0.002, p = .962$ ) nor motion sensitivity ( $F_{1,49} = 0.196, p = .747$ ).

ssVEP power at 10 Hz differed significantly across groups ( $F_{1,53} = 18.36, p < .0001$ ), with a reduction in patients with SZ ( $p = .028$ ) but an increase in ASD subjects ( $p = .007$ ) relative to CNs (Figure 2C, Table 1). Across groups, ssVEP power predicted FER ( $F_{1,47} = 4.66, p = .016$ ), with no significant difference in the slopes ( $F_{2,47} = 1.83, p = .172$ ). Motion sensitivity was not predicted by ssVEP ( $F_{1,49} = 0.77, p = .782$ ).

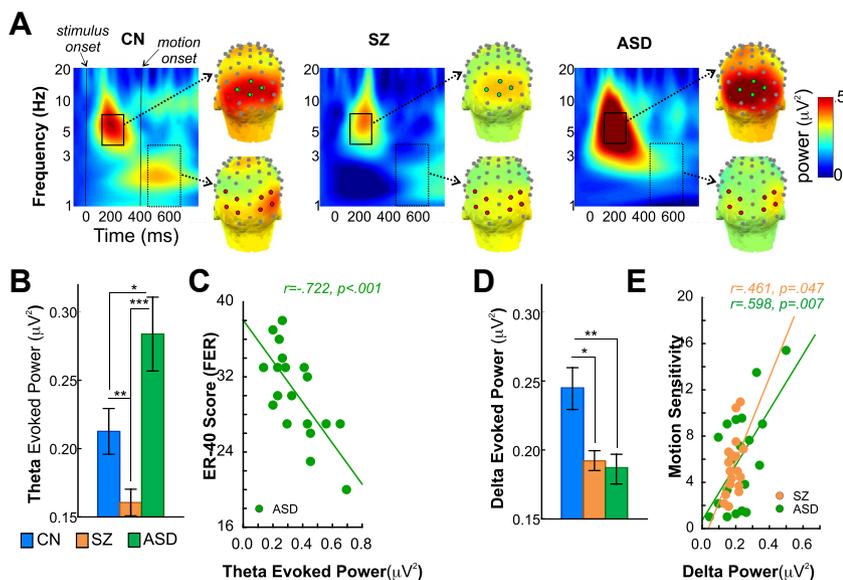
### Functional MRI

During scanning, target detection ( $F_{2,53} = 0.08, p = .924$ ) and false alarm ( $F_{2,53} = .49, p = .614$ ) rates were equivalent across groups (Supplemental Table S1).

**Table 1. Electrophysiological Measures**

EEG Measure	Amplitude ( $\mu$ V)			Main Effects				
	CN	SZ	ASD	Group	Hemisphere	Stimulus	Group $\times$ Hemisphere	Group $\times$ Stimulus
Theta	0.21 $\pm$ 0.07	0.16 $\pm$ 0.04	0.28 $\pm$ 0.11	$F_{2,53} = 10.27, p = .0002$	-	$F_{2,52} = 36.39, p < .0001$	-	$F_{4,104} = 3.28, p = .014$
Delta								
Left hemisphere	0.22 $\pm$ 0.09	0.19 $\pm$ 0.05	0.16 $\pm$ 0.06	$F_{2,53} = 6.20, p = .004$	$F_{1,53} = 3.23, p = .078$	$F_{2,52} = 17.76, p < .0001$	$F_{2,53} = 0.754, p = .475$	$F_{4,104} = 1.94, p = .108$
Right hemisphere	0.26 $\pm$ 0.09	0.19 $\pm$ 0.04	0.20 $\pm$ 0.08					
Alpha ERD								
Left hemisphere	-0.12 $\pm$ 0.13	-0.04 $\pm$ 0.09	-0.27 $\pm$ 0.26	$F_{2,53} = 8.91, p = .0005$	$F_{1,53} = 4.33, p = .042$	$F_{2,52} = 4.69, p = .013$	$F_{2,53} = 3.52, p = .036$	$F_{4,104} = 1.77, p = .140$
Right hemisphere	-0.15 $\pm$ 0.22	-0.03 $\pm$ 0.11	-0.45 $\pm$ 0.53					
ssVEP	0.13 $\pm$ 0.09	0.03 $\pm$ 0.03	0.24 $\pm$ 0.16	$F_{2,53} = 18.36, p < .0001$	-	$F_{2,52} = 0.291, p = .748$	-	$F_{4,104} = 0.200, p = .937$

Values are mean  $\pm$  SD. ssVEP measures were taken from midline electrode sites. ASD, autism spectrum disorder group; CN, control group; EEG, electroencephalogram; ERD, event-related desynchronization; ssVEP, steady-state visual evoked potential; SZ, schizophrenia group.



**Figure 1.** (A) Time-frequency and scalp topography maps of evoked power to stimulus and motion onset. Time-frequency plots and scalp topography of mean evoked power (average of all stimuli) for the control subject (CN), schizophrenia (SZ), and autism spectrum disorder (ASD) groups. For each stimulus type, theta power (4–7 Hz) was tested during the latency window 150–250 ms (solid rectangle) following stimulus onset at time 0 and measured across 4 midoccipital electrode sites from the specially developed Duke system featuring equidistant spacing between electrodes (7Z, 8Z, 8L, 8R) (green circles). Delta (1–4 Hz) activity was tested between 50 and 250 ms (dashed rectangle) interval following the onset of motion (at time 400 ms) across 4 bilateral lateral-occipital sites (8L/8R, 5LB/5RB, 9L/9R, 5LC/5RC) (red circles). (B) Theta evoked power, group differences. Bar plots of mean theta power (collapsed across stimulus type) for each participant group. Theta activity was significantly lower in patients with SZ compared with CNs. In contrast, theta was significantly elevated in ASD participants. Asterisks denote statistical significance as follows: \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ . (C) Correlation of Penn Emotion Recognition Task (ER-

40) scores and theta evoked power. In ASD subjects, enhanced theta activity significantly correlated with impaired face emotion recognition (FER). This correlation was not significant in either SZ ( $r = -.36, p = .135$ ) or CN ( $r = -.32, p = .240$ ) groups. (D) Delta evoked power, group differences. Bar plots of mean delta power (collapsed across stimulus type) for each participant group. In contrast to theta, delta power was significantly lower in both the SZ and ASD groups compared with the CN group. (E) Correlation between motion sensitivity and delta evoked power. In both clinical groups, reduced delta power correlated with behavioral measures of impaired motion sensitivity. This correlation was not significant in CNs ( $r = .38, p = .131$ ).

Across hemispheres and cortical/subcortical regions, there were no significant effects of group membership ( $F_{2,53} = 2.82, p = .068$ ). However, there was a significant main effect of region ( $F_{5,49} = 43.62, p < .001$ ) and a group  $\times$  region interaction ( $F_{10,98} = 2.86, p < .004$ ) (Figure 3A). The main effect of hemisphere was significant ( $F_{1,53} = 6.03, p = .017$ ) but did not interact with group ( $F_{2,53} = 1.21, p = .303$ ) or region ( $F_{5,49} = 1.66, p = .163$ ); therefore, within-region analyses were collapsed across hemispheres.

In the MTC region, activation was reduced in patients with SZ ( $F_{1,34} = 4.84, p = .034$ ) and ASD participants ( $F_{1,35} = 4.00, p = .043$ ) compared with CNs (Figure 3B, Supplemental Table S2). ASD participants, however, had significantly greater activation in the early visual and dorsal regions compared with patients with SZ (early visual [ $F_{1,37} = 4.63, p = .039$ ], dorsal [ $F_{1,37} = 4.25, p = .047$ ]) and CNs (early visual [ $F_{1,35} = 5.79, p = .022$ ], dorsal [ $F_{1,35} = 4.23, p = .048$ ]). Activation of V1 was equivalent in the ASD and CN ( $F_{1,35} = 0.19, p = .663$ ) groups but was reduced in patients with SZ relative to both CNs ( $F_{1,34} = 6.68, p = .014$ ) and ASD participants ( $F_{1,37} = 7.19, p = .011$ ). There were no significant group differences within the ventral region.

Subcortically, activation of the pulvinar nucleus was significantly reduced in patients with SZ ( $F_{1,34} = 6.29, p = .017$ ) but not in ASD subjects ( $F_{1,35} = 0.13, p = .715$ ) compared with CNs (Figure 3C, D).

**Correlations With EEG.** Based on our previous study (31), activation within the dorsal, MTC, and pulvinar regions were correlated with EEG measures (theta, delta, ERD, ssVEP). In ASD subjects, enhanced theta band activity correlated with increased dorsal activation ( $r = .61, p = .004$ )

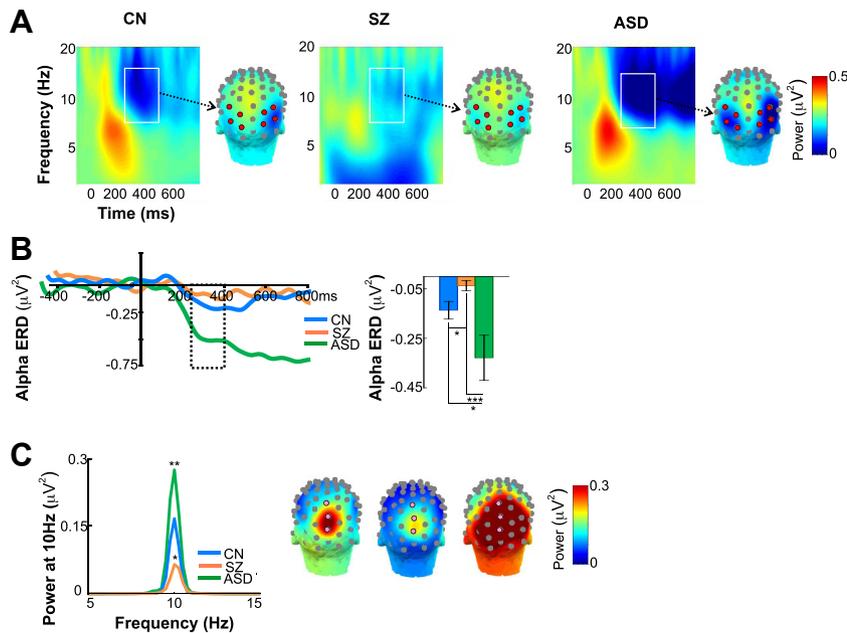
(Figure 3E). In parallel, delta activity to stimulus motion correlated with activation within the MTC (CN [ $r = .66, p = .004$ ], SZ [ $r = .48, p = .038$ ], and ASD [ $r = .52, p = .019$ ] groups). Finally, reduction in alpha ERD in SZ ( $r = -.48, p = .038$ ) as well as its increase in ASD ( $r = -.61, p = .004$ ) correlated with the magnitude of pulvinar activation (Figure 3F). Exploratory correlations ( $n = 9$ ) between EEG measures and activation within the V1, early visual, and ventral regions were nonsignificant within or across subject groups (all  $p > .250$ ).

**Resting-State Functional Connectivity.** Mean resting-state functional connectivity (rsFC) across all regions differed significantly across groups ( $F_{2,53} = 11.81, p < .001$ ) (Figure 4A). The group  $\times$  region interaction was also significant ( $F_{10,98} = 2.48, p = .011$ ).

Compared with CNs, mean rsFC of V1 ( $F_{1,34} = 7.27, p = .011$ ), early visual ( $F_{1,34} = 8.26, p = .007$ ), dorsal ( $F_{1,34} = 7.86, p = .008$ ), ventral ( $F_{1,34} = 23.90, p < .001$ ), and MTC ( $F_{1,34} = 7.69, p = .009$ ) regions (to all other regions) was reduced in patients with SZ, whereas mean rsFC of the pulvinar to cortex ( $F_{1,34} = 0.64, p = .802$ ) was equivalent.

In ASD, mean cortical rsFC was similar to that of CNs ( $p > .6$  for all). Subcortically, however, rsFC between pulvinar and the mean of all cortical regions was significantly greater in ASD subjects compared with CNs ( $F_{1,35} = 6.21, p = .017$ ) and patients with SZ ( $F_{1,37} = 8.03, p = .007$ ).

In pairwise comparisons (Figure 4B), reduced rsFC in SZ was observed primarily in the ventral and MTC regions. By contrast, in ASD, increased rsFC was observed especially between the pulvinar and dorsal regions.



**Figure 2.** (A) Single-trial time-frequency histograms and scalp topography maps of event-related desynchronization (ERD) of alpha activity. Time-frequency plots and scalp topography of mean alpha ERD single-trial power for each participant group. Alpha ERD was measured between 7 and 14 Hz over the latency window of 250–400 ms post-stimulus onset (white rectangles) across 4 bilateral lateral-occipital electrodes (8L/8R, 5LB/5RB, 9L/9R, 5LC/5RC) (red circles). (B) Time course and amplitude of alpha ERD. In the test interval of 250–400 ms (dashed rectangle) ERD amplitude was significantly reduced in patients with schizophrenia (SZ) compared with control subjects (CNs). In contrast, the ERD was enhanced in the autism spectrum disorder (ASD) group compared with both the SZ and CN groups. ERD enhancement persisted in ASD subjects relative to the CN and SZ groups. (C) Counterphase reversals at 10 Hz. Tracings are of group-averaged steady-state visual evoked potential power collapsed across stimulus types and plotted by spectral frequency. Relative to CNs, steady-state visual evoked potential amplitude was reduced in patients with SZ and enhanced in ASD subjects. Asterisks denote significance of the difference between patients with SZ and ASD subjects compared with CNs, \* $p < .05$ , \*\* $p < .01$ , \*\*\* $p < .001$ . The steady-state visual evoked potential was tested across 3 midoccipital electrodes (6Z, 7Z, 8Z).

Finally, the relationship between pulvinar rsFC and EEG alpha measures was tested in preplanned correlations (31). In participants with ASD, but not in CNs ( $r = -.06$ ,  $p = .832$ ) or patients with SZ ( $r = -.38$ ,  $p = .113$ ), the amplitude of alpha ERD correlated with mean connectivity between the pulvinar and cortex ( $r = -.53$ ,  $p = .015$ ) (Figure 4C).

**Classification Analyses.** The discriminative power of physiological variables (4 EEG, 6 fMRI, 2 rsFC) on classification of ASD and SZ participants was assessed using RF. The out-of-bag classification accuracy was 97.4%, with correct classification of all SZ patients and 19 of 20 ASD participants. Four variables (theta, ssVEP, ERD, and mean cortical rsFC) were significantly ( $p < .01$ ) important for classification (Supplemental Table S3). When all 3 groups were entered into the RF analysis, classification accuracy was 82.1%; however, patients with SZ and ASD subjects were classified with 100% and 94.12% accuracy, respectively.

To compare the discriminative efficacy of multimodal versus unimodal variables, RF was conducted with only EEG or fMRI variables. Using EEG measures alone, classification accuracy between SZ and ASD dropped to 74.4%. With only fMRI variables, accuracy was 69.2%.

**Correlations With Behavior and Symptoms.** Stepwise regression was used to evaluate the relationship among all measures of visual processing together and FER. Across groups, the variables significantly predicted FER ( $F_{1,51} = 12.12$ ,  $p = .001$ ). Given the observed heterogeneity of slopes between key physiological measures and FER, within-group analyses covarying against FER were conducted.

In CNs, there was a strong association between sensory-processing measures and FER (adjusted  $R^2 = .653$ ) with both

motion sensitivity ( $r_p = .78$ ,  $p < .001$ ) and mean cortical rsFC ( $r_p = .64$ ,  $p = .002$ ) as significant independent predictors ( $F_{2,12} = 14.19$ ,  $p < .001$ ).

In ASD participants, the combined measures accounted for ~64% of the variance in FER (adjusted  $R^2 = .635$ ). Significant predictors of FER impairment were theta activity ( $r_p = -.59$ ,  $p < .001$ ) and motion sensitivity ( $r_p = .39$ ,  $p = .014$ ) ( $F_{2,16} = 16.64$ ,  $p < .001$ ).

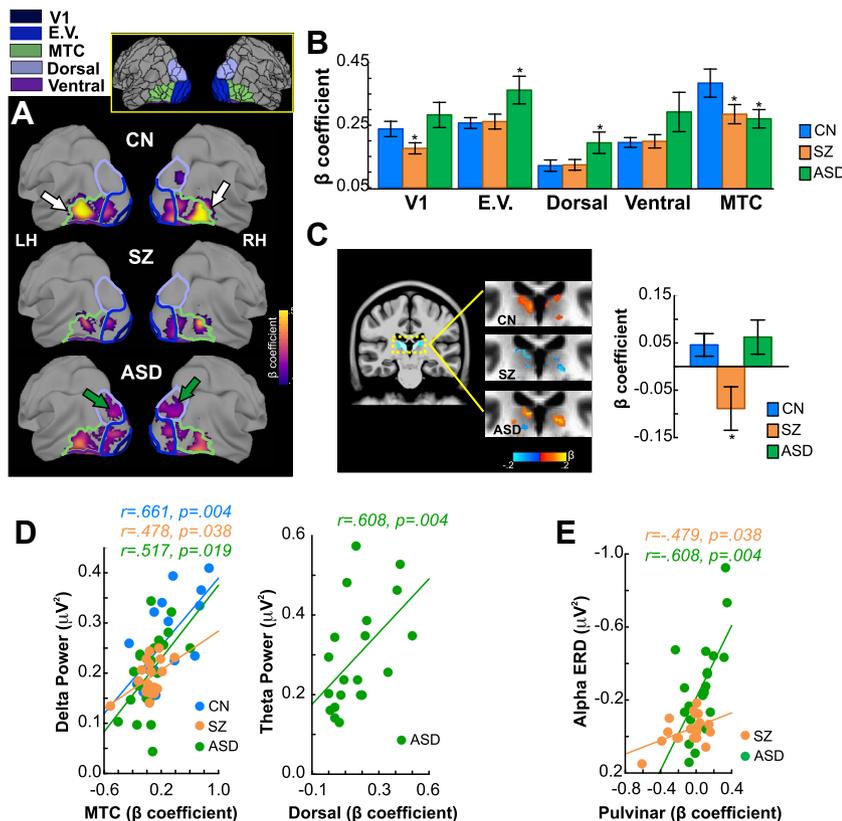
In patients with SZ, ~45% of the variance in FER (adjusted  $R^2 = .445$ ) was accounted for by the combined measures. Alpha activity ( $r_p = .54$ ,  $p = .008$ ), activation of the V1 ( $r_p = -.53$ ,  $p = .008$ ), and mean rsFC of the pulvinar ( $r_p = -.39$ ,  $p = .043$ ) were significant independent predictors ( $F_{3,15} = 5.80$ ,  $p = .007$ ).

Exploratory correlations ( $n = 18$ ) evaluated the relationship between physiological variables and clinical symptoms in SZ and ASD. In both groups, abnormal alpha ERD was associated with greater clinical symptoms. In SZ, alpha ERD correlated inversely with Positive and Negative Syndrome Scale (negative scale) ( $r = .51$ ,  $p = .027$ ), and in ASD, ERD amplitude correlated directly with the Autism Diagnostic Observation Schedule, Second Edition, social interaction rating ( $r = -.62$ ,  $p = .003$ ) (Supplemental Figure S3). Similarly, the Autism Diagnostic Observation Schedule, Second Edition, rating correlated with ssVEP power ( $r = .45$ ,  $p = .048$ ).

No significant relationship was observed between medication dose (chlorpromazine equivalents) and any behavioral/physiological measure in SZ patients (all  $p > .25$ ).

## DISCUSSION

The ability to recognize intended emotions based upon facial expression is a critical component of human social interaction and is impaired in both SZ and ASD. In SZ, we have previously observed that deficits in early visual processing contribute to



**Figure 3.** (A) Group-averaged functional magnetic resonance imaging activation for the contrast of moving vs. static stimuli. For each participant group, mean activation is shown on the semi-inflated fsaverage brain. Colored outlines are boundaries of the 5 cortical regions included in analyses (V1: dark blue; early visual [E.V.]: blue; dorsal: purple; ventral: violet; middle temporal complex [MTC]: green). Each region consists of between 1 and 9 individual parcels [total of 26; see supplement in Glasser *et al.* (18) and Supplemental Table S1]. Inset shows all parcels (drawn in black) of the Human Connectome Project Multimodal Parcellization atlas, including the parcels comprising the 5 regions (colored) from which data were extracted and averaged. Single-participant statistical analyses followed general linear model procedures incorporated in AFNI (afni\_proc.py). Group differences in activation were evaluated by analysis of variance using AFNI's 3dMVM program. Corrections for multiple comparisons were carried out at the cluster level using Monte Carlo simulation (AFNI's slow\_surf\_clustsim.py;  $p < .01$ , corrected). Arrows (on control subject [CN] maps) point to the MTC region where activation was significantly higher in CNs compared with both patients with schizophrenia (SZ) and autism spectrum disorder (ASD) participants. Green arrows (on ASD maps) point to the dorsal region that showed enhanced activation in ASD participants. (B) Mean beta contrast parameter estimates within each region. Asterisks denote regions where activations in patients with SZ or ASD participants differed significantly from that of CNs,  $*p < .05$ . Activation of the MTC region was reduced in both patients with SZ and ASD participants. These

reductions were localized within the MST, MT, LO1, and LO3 parcels of the HCP-MMP atlas. In ASD participants, activation within both E.V. and dorsal stream regions was significantly greater compared with both patients with SZ and CNs. The enhanced E.V. activations were located within the V2 and V3 parcels and the dorsal stream region with increased activation localized to the V3A parcel. (C) Mean activation within the pulvinar nucleus of the thalamus. Subcortically, pulvinar activation was reduced in patients with SZ relative to CNs (dashed rectangle on sagittal slice indicates magnified region shown to the right). (D) Correlations with electroencephalogram variables. In all participant groups, greater activation within the MTC regions was significantly associated with increased delta evoked power elicited by the motion onset of all stimuli (left). In ASD participants, enhanced activation of the dorsal region correlated with participants' abnormally high theta power following stimulus onset (right). (E) Correlation of pulvinar activation with alpha event-related desynchronization (ERD). In both patients with SZ and ASD participants, the magnitude of pulvinar activation correlated significantly with ERD amplitude. Note that the vertical scale is reversed to show that such that larger (more negative) alpha ERD is associated with greater pulvinar activation. LH, left hemisphere; RH, right hemisphere.

impaired FER (31). In the present study, ASD and SZ groups showed equivalent FER impairments; however, the underlying patterns of visual processing dysfunction contributing to these deficits differed substantially, permitting 97% discrimination between groups. In SZ, deficits were attributable to reduced sensory activation, as reported previously (31,52). By contrast, in ASD, increased sensory-driven responses predicted impaired FER. In addition to reaffirming the importance of visual sensory deficits to higher-order cognition in SZ and ASD, these findings highlight the ability of convergent EEG and fMRI-based measures to distinguish between disorders.

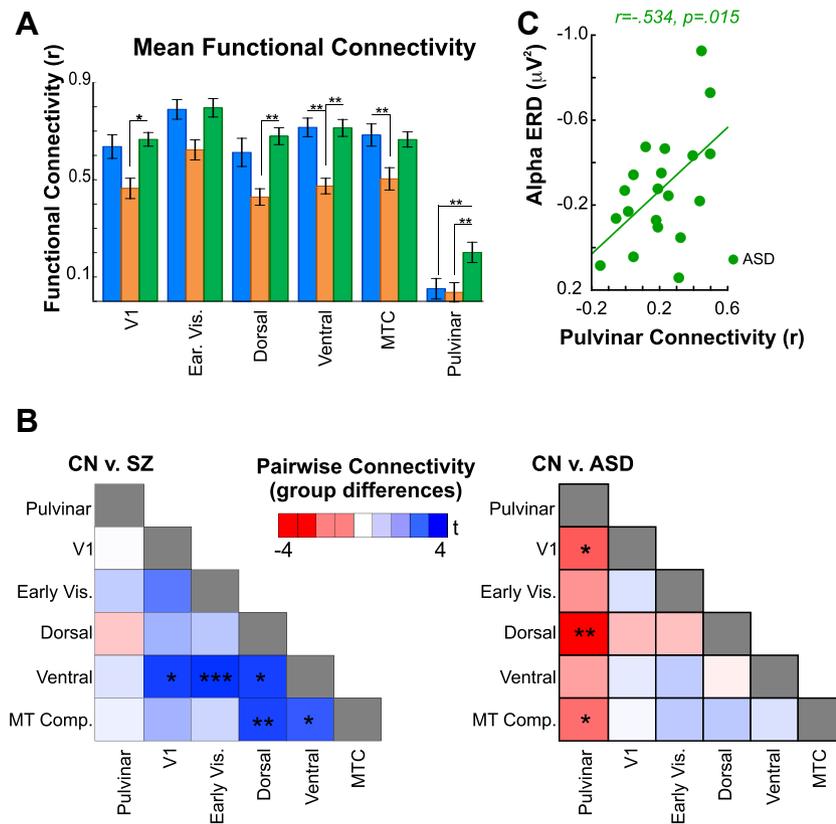
### Electrophysiology

Electrophysiological measures included theta frequency responses to stimulus onset, delta frequency responses to motion onset, and alpha ERD/ssVEP. Consistent with prior findings by our group (31,53) and others (54,55), significant reductions across all measures were observed in SZ. In ASD, delta responses were similarly reduced and correlated with impaired motion sensitivity. However, theta and alpha responses were

markedly enhanced, consistent with previous findings (56,57). The alpha ERD, in particular, was elevated and prolonged and may represent a physiological substrate for the clinical observation that ASD individuals struggle to disengage from visual stimuli (58,59). Finally, both the reductions in alpha amplitude in SZ and the excesses in ASD, correlated with symptom severity, suggesting that either hypo- or hyperengagement could undermine FER and, by extension, social function.

### Neuroimaging

In addition to EEG, fMRI measures were obtained during resting state and visual stimulation. As with electrophysiology, convergent and divergent patterns of dysfunction were observed across groups. Specifically, both clinical groups showed convergent deficits in MTC activation that correlated with the convergent deficit in delta evoked power. By contrast, divergent patterns in other visual regions were observed, such that patients with SZ showed a decrease in activation in V1, whereas ASD subjects showed increased activation across the



**Figure 4.** (A) Resting-state functional connectivity (rsFC). Bar graphs are of mean connectivity between each region and the average of all others. Compared with control subjects (CNs), mean rsFC was reduced in patients with schizophrenia (SZ) in the ventral and middle temporal cortex (MTC) regions. Compared with participants with autism spectrum disorder (ASD), patients with SZ had reduced rsFC in the V1, dorsal, and ventral regions. In contrast, mean rsFC of all cortical regions was equivalent in ASD participants compared with CNs. Mean rsFC of the pulvinar, however, was significantly greater in ASD subjects relative to both CNs and patients with SZ. (B) Group differences in pairwise rsFC. For each participant, rsFC between regions was calculated in a pairwise fashion and entered into between-group (2-tailed) *t* tests. Resulting *t* values are plotted in heatmaps comparing CNs with patients with SZ (left) and CNs with ASD participants (right). Blue scale denotes greater rsFC in CNs vs. patients with SZ and lower rsFC in CNs compared with ASD participants (thus, red scale denotes greater rsFC in ASD participants relative to CNs). (C) Correlation of pulvinar connectivity and alpha event-related desynchronization (ERD). In ASD participants, greater alpha ERD amplitude was associated with increased mean connectivity between pulvinar and cortex. \**p* < .05, \*\**p* < .01, \*\*\**p* < .001.

early visual and dorsal regions, which correlated selectively to the increased theta activity observed electrophysiologically.

Differential patterns were also observed in resting-state fMRI analyses, with patients with SZ showing reduced connectivity between visual regions and ASD participants showing normal cortical connectivity but markedly enhanced connectivity between the pulvinar and visual cortex, which, in turn, significantly predicted enhanced alpha ERD. Increased pulvinar-visual cortex connectivity has been reported in ASD (36); however, to our knowledge, pulvinar activation or pulvinar-cortical connectivity relative to alpha modulation has not been previously investigated.

### Implications for Pathophysiology

Deficits in visual sensory function in SZ and ASD are proposed to reflect altered excitation/inhibition balance [reviewed in Foss-Feig *et al.* (60) and Krystal *et al.* (61)]. In SZ, excess developmental pruning (62) may lead to a hypoglutamatergic state particularly involving impaired *N*-methyl-D-aspartate function (63). Visual deficits, which preferentially involve magnocellular-system dysfunction (64), are consistent with patterns induced by *N*-methyl-D-aspartate receptor antagonists such as ketamine (65). In ASD, both “hypopruning” (66) of glutamatergic systems and underfunction of gamma-aminobutyric acid–mediating signaling (67,68) have been proposed and may interrelate with deficits in visual perceptual processes (69). The patterns observed here of reduced power and activation across all

measures in SZ are consistent with reduced excitation throughout the visual system. Such deficits would lead to impaired sensory processing and are consistent with prevailing *N*-methyl-D-aspartate receptor hypofunction models [reviewed in Javitt (29) and Marin (70)] and concepts of underdevelopment (71) and hyperpruning of cortical glutamatergic terminals (62).

By contrast, patterns in ASD were of both hypo- and hyperresponsivity in EEG and fMRI measures, as well as increased pulvinar-cortex connectivity and increased/prolonged stimulus-related alpha suppression. This pattern is consistent with either disrupted cortical inhibition (72,73) or cortical overgrowth/reduced synaptic pruning (66,71). We have recently observed that the amplitude of the visual theta response declines progressively during childhood/late adolescence (74), mirroring the pruning-induced synapse reduction in the visual cortex during that time period (75). Thus, in ASD, the present findings are compatible with underpruning and persistence of early childhood patterns into adolescence and adulthood, whereas findings of reduced theta amplitude in SZ (below those of age-matched CNs) are consistent with hyperpruning (31,74,76).

The present study also highlights the potential involvement of the pulvinar nucleus in sensory-level impairments in ASD. The pulvinar is thought to play a critical role in cortical integration of visual information via modulation of alpha rhythms (77). Abnormalities of the pulvinar have been observed previously in ASD (28,78) but have not been a primary research focus. The present findings of enhanced and prolonged ERD,

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along with increased alpha ssVEP, suggest the need for increased use of single-trial, rather than average, EEG approaches for evaluating neurophysiological deficits in both SZ and ASD and for greater focus on the investigation of potential pulvinar pathology.

### Implications for Diagnosis and Management

Across neuropsychiatric disorders, similar deficits at the behavioral level may result from differential underlying pathological mechanisms. To date, physiological measures are incorporated into diagnostic/management algorithms to only a limited degree. In the present study, leveraging of neurophysiological and neuroimaging-based measures through a machine-learning approach obtained close to 100% separation between patients with SZ and ASD participants, encouraging further use of sensory-level multimodal approaches for patient classification. Sensory-level measures are well suited for diagnostic use, given that they are highly consistent across control individuals and require only limited participant engagement to collect, in some cases, using routine clinical equipment. If the present results are confirmed in larger samples, measures of this type might be useful in guiding treatment, cognitive remediation, or noninvasive brain stimulation-type interventions.

### Limitations

Although differences between groups were statistically robust, they require replication in larger samples. In particular, both SZ and ASD are characterized by substantial heterogeneity that is difficult to parse in samples of this size. Further, the ASD group was limited to adults with IQ >70, and future studies should evaluate neurophysiological measures across the full spectrum of ASD and across the developmental life span.

While deficits did not correlate with medication dose, patients with SZ were receiving antipsychotics, whereas ASD participants were medication free; thus, a medication effect cannot be excluded. Finally, eye tracking was not obtained in this study, and deficits in SZ could be related to lack of sustained fixation. Given the interleaved nature of the task, however, poor fixation cannot explain the discrepancy between increased stimulus-onset responses but reduced motion-onset responses in ASD. Last, while the RF analysis uses a cross-validation method, the sample size did not permit the use of separate training and test datasets.

### Conclusions

Both SZ and ASD are increasingly associated with perturbed sensory function that contributes to impaired social functioning but that may stem from differential underlying pathophysiological mechanisms. Using a multimodal imaging approach, we demonstrate a primarily hypoactive state in SZ and a mixed pattern of hyper- and hypoactivation in ASD. These findings highlight the importance of physiologically based measures in guiding etiological and interventional studies in neuropsychiatry.

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