Out-of-Synch and Out-of-Sorts: Dysfunction of Motor-Sensory Communication in Schizophrenia

Judith M. Ford, Brian J. Roach, William O. Faustman, and Daniel H. Mathalon

Background: Phase synchronization of neural activity preceding a motor act may reflect an efference copy of the motor plan and its expected sensory consequences (corollary discharge), which is sent to sensory cortex to herald the arrival of self-generated sensations and dampen the resulting sensory experience. We performed time-frequency decomposition of response-locked electroencephalogram (EEG) to examine phase synchronization of oscillations across trials (phase-locking factor [PLF]) to self-paced button presses. If prepress PLF reflects the activity in motor cortex, it should be contralateralized. If it reflects the action of the efference copy, it should be related to subsequent sensory suppression. If efference copy/corollary discharge mechanisms are abnormal in schizophrenia, it should be reduced in patients with schizophrenia.

Methods: Electroencephalogram was collected while 23 patients (20 schizophrenia; 3 schizoaffective) and 25 age-matched control subjects pressed a button, at will, every 1 to 2 sec. Phase-locking factor preceding and following button presses was calculated from single-trial EEG; averaging single trials yielded response-locked event-related potentials (ERPs) to the tactile response associated with button pressing.

Results: Consistent with its hypothesized reflection of efference copy/corollary discharge signals, prepress gamma band neural synchrony was 1) maximal over the contralateral sensory-motor cortex in healthy subjects, 2) correlated with the ipsilateralized somatosensory ERP amplitude evoked by the press, and 3) reduced in patients. Prepress neural synchrony in the beta band was also reduced in patients, especially those with avolition/apathy.

Conclusions: These data are consistent with dysfunction of forward model circuitry in schizophrenia and suggest that the specific motor-sensory system affected is selectively linked to symptoms involving that system.

Key Words: Corollary discharge, EEG, motor, neural oscillations, schizophrenia

A forward model system involving transmission of an efference copy of motor commands to sensory cortex to generate corollary discharges that prepare it for impending sensory consequences of self-initiated motor acts has been described as a mechanism that helps us unconsciously disregard sensations resulting from our own actions as we maneuver through our environment. Helmholtz (1) first described a forward model mechanism that allows us to discriminate between moving objects and movements on the retina resulting from eye movements. Von Holst and Mittelstadt (2) and Sperry (3) later suggested that a motor action is accompanied by an efference copy of the action that produces a corollary discharge representation of its expected sensory consequences in sensory cortex.

Although not always couched in terms of a forward model, evidence is emerging that perception is accomplished by a dynamic matching of sensory expectations with sensory input in a combined top-down/bottom-up fashion (4). Coordination between neural populations or cortical regions may be self-organizing (5), with temporal synchronization between firing rates of spatially segregated and distributed neuronal assemblies being an emergent property of neural networks. Thus, top-down processes such as selective attention (6) enhance the phase locking of neural oscillations at specific frequency bands to incoming stimuli, promoting enhanced perception.

Similarly, the forward model may involve a dynamic matching of incoming sensory signals with experience-shaped libraries of percepts. It has been suggested that the synchronization of ongoing neural oscillations by the stimulus may reflect binding of separately processed and neuroanatomically segregated stimulus features with each other and with expectations (7). Perceptual enhancement associated with attention is adaptive, whereby organisms can quickly evaluate and categorize potentially important environmental events. However, unlike the poststimulus synchronization of neural oscillations that occur in response to environmentally generated sensory input, the sensory expectancies or corollary discharges associated with motor acts precede the self-generated reafferent inputs to sensory cortex and are subtracted from them once they arrive (8).

Because the forward model mechanism involves coordinated motor-sensory communication, enhancement of neural synchrony might be evident prior to execution of motor acts. In fact, local field potential recordings from somatosensory cells in rats showed neural synchrony preceding exploratory whisking in the 7 to 12 Hz (9) and 30 to 35 Hz (10) bands, perhaps triggered by the transfer of an efference copy of motor preparation to somatosensory cortex, seen as oscillations occurring several hundred milliseconds before the action.

Failures of the corollary discharge (11) or forward model mechanism (12) may contribute to self-monitoring deficits and some symptoms of schizophrenia. If efference copies of willed intentions do not produce corollary discharges of their expected sensory consequences, patients with schizophrenia may fail to recognize that they are the source of their own actions, resulting

From the Psychiatry Service (JMF, BJR, DHM), Veterans Affairs Connecticut Healthcare System, West Haven, and Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut; and Psychiatry Service (WOF), Veterans Affairs Palo Alto Healthcare System, Palo Alto, and Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California.

Address reprint requests to Judith M. Ford, Ph.D., Department of Psychiatry, Yale University School of Medicine, 950 Campbell Avenue, VA CT Healthcare System, 116A, West Haven, CT 06517; E-mail: Judith.ford@yale.edu.

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in feelings of being controlled by outside forces. On a more basic level, this failure could also result in poor online, millisecond-to-millisecond correction of movements, and motor awkwardness typical of the illness might result (13). Ultimately, abnormal kinesthetic experiences may diminish the motivation for action.

Behavioral and electrophysiological evidence for corollary discharge dysfunction in schizophrenia is growing. Using the N1 component of the event-related potential (ERP), we showed that auditory cortical response dampening observed in control subjects during talking was not evident in patients with schizophrenia (14). Deficits in self-monitoring of action may also underlie the failure of schizophrenic patients to correct action errors when only proprioceptive feedback is available (15). The normal attenuation of sensation from self-produced touch was not as evident in patients with hallucinations and/or passivity experiences (16), patients with negative symptoms who had failures of willed actions (17), and patients demonstrating sensory prediction deficits during movements (18). All could result from a dysfunction of the corollary discharge system and/or associated insufficient suppression of the sensory reafference.

Given the close temporal proximity of corollary discharge signals and the subsequent sensory reafference, real-time measures of neural signals, such as electroencephalogram (EEG) and ERPs, are needed to examine neural activity preceding, during, and following the action. Recently, time-frequency decomposition of event-locked single-trial EEG epochs has been developed for finer-grained examination of neural oscillations across both frequency and time domains. Phase-locking factor (PLF) (19) estimates phase synchronization of neural oscillations across individual event-locked EEG epochs, at specific frequencies, independent of power. It reflects temporal phase coherence of oscillations with respect to an event, across trials, and is different from spatial EEG coherence (20) or spatial phase coherence (21), which are calculated between different electrode sites. Neural synchrony may be involved in mechanisms of sensorimotor integration and provide voluntary motor systems with continually updated feedback on performance (22).

Also of interest in studies of the corollary discharge is suppression of the neural response to the sensory reafference following a self-initiated action. While phase resetting to the onset of an external stimulus may reflect sensation (23), early components of the averaged ERP are traditionally used to assess gating of sensation preceding and during motor movements (24–31). For example, Rossini *et al.* (30) noted that early (<50 msec) somatosensory ERPs to median nerve shocks are reduced contralaterally, but not ipsilaterally, during motor movement conditions compared with conditions with no motor movement, suggesting that the gating of sensation is specific to the contralateral hemisphere. Thus, ample evidence shows that the somatosensory ERP is relatively ipsilateralized when a somatosensory stimulus is delivered to a limb during self-generated movement, compared with the contralateralized response observed when the stimulus is delivered to a stationary limb. On the basis of this literature and the theoretical argument that contralateral suppression of the somatosensory ERP during movement reflects the action of an efference copy/corollary discharge mechanism, we subtracted the postbutton-press somatosensory ERP measured over sites contralateral to the response hand from the ERP measured ipsilateral to the response hand and reasoned that the degree of ipsilateralization (i.e., reduced contralateralization) reflects the degree of corollary discharge-mediated somatosensory suppression. If true, we hypothesized that this relative ipsilateralization would be less evident in schizophrenia (due to their presumed corollary discharge dysfunction) and would be directly related to the strength of prepress measures of the efference copy, at least in normal subjects. Thus, by positing on theoretical grounds that a prepress efference copy signal should be directly related to the ipsilateralization of the postpress ERP, we set criteria for evaluating our hypothesis that prepress neural synchrony reflects the efference copy signal that is instrumental in predicting and dampening the (somato) sensory consequences of our own motor acts.

Current Approach

Our first goal in this study was to quantify the synchrony of neural events associated with the hypothesized efference copy during initiating a button press. Because of the contralateral organization of the sensorimotor system, we hypothesized that an efference copy of a planned action should arise in contralateral, but not ipsilateral, motor cortex and be apparent before but not after an action. Accordingly, we compared trial-to-trial synchronous neural activity preceding and following a button press from contralateral and ipsilateral sites.

Our second goal was to relate possible measures of the efference copy to subsequent suppression of sensory reafference. If the contralateralized prepress neural synchrony were a reflection of the efference copy, it should be related to postpress suppression of the tactile experience associated with pressing the button. Accordingly, we related prepress synchrony to postpress ERP suppression.

Our third goal was to assess deficits in the efference copy in patients with schizophrenia. To the extent that prepress neural synchrony reflects the efference copy and to the extent that patients have abnormalities in the efference copy, we hypothesized that they would have deficits in prepress neural synchrony. We compared prepress and postpress synchrony from contralateral and ipsilateral sites in control subjects and patients with schizophrenia.

Our fourth goal was to relate motor system efference copy abnormalities to symptoms in the motor domain. To the extent that prepress neural synchrony reflects the efference copy in the motor system, we hypothesized that prepress neural synchrony would be especially reduced in patients with deficits in the initiation of actions, such as avolition and apathy, and delusions that their motor actions were not their own, such as delusions of control.

Methods and Materials

Participants

Electroencephalogram data were acquired from 24 patients and 26 healthy comparison subjects. All gave written informed consent after procedures had been fully described. Data from one patient and one control subject contained high-frequency noise and were dropped from the analysis. Demographic and clinical data for the remaining subjects are summarized in Table 1.

Patients were recruited from community mental health centers and inpatient and outpatient services of the Veterans Affairs Healthcare System in Palo Alto and San Francisco, California. All were on stable doses of antipsychotic medications and met DSM-IV (32) criteria for schizophrenia ($n = 20$) or schizoaffective disorder ($n = 3$) based on a Structured Clinical Interview for DSM-IV (SCID) (33) conducted by a clinical psychologist or a SCID conducted by a clinically trained research assistant followed by a clinical interview with a clinical psychologist. Patients meeting DSM-IV criteria for alcohol or drug abuse within 30 days