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Minireview

The function of efference copy signals: Implications for symptoms of schizophrenia

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ABSTRACT

Efference copy signals are used to reduce cognitive load by decreasing sensory processing of reafferent information (those incoming sensory signals that are produced by an organism's own motor output). Attenuated sensory processing of self-generated afferents is seen across species and in multiple sensory systems involving many different neural structures and circuits including both cortical and subcortical structures with thalamic nuclei playing a particularly important role. It has been proposed that the failure to disambiguate self-induced from externally generated sensory input may cause some of the positive symptoms in schizophrenia such as auditory hallucinations and delusions of passivity. Here, we review the current data on the role of efference copy signals within different sensory modalities as well as the behavioral, structural and functional abnormalities in clinical groups that support this hypothesis.

1. Introduction

Of the vast majority of sensory information with which our central nervous system is inundated, only a small portion receives our attentional capacities and ever reaches conscious awareness. Sensory gating is a complex process whereby sensory information is processed with extraneous information being filtered out. The end result of this is an experience of the external world that is computed from a number of different sensory signals to allow for the understanding of environmental stimuli and the generation of an appropriate behavioral response. Thus, sensory information is not passively perceived but transformed in many stages of active processing. Failures in different types of sensory gating may play a causal role in symptoms of different psychopathologies. For instance, efficient sensory processing requires a comparator mechanism, ensuring actual sensory feedback matches expected feedback. To achieve this, sensorimotor systems are thought to make use of a 'forward model', whereby information about motor output is used to generate predicted reafferents that modulate the response of sensory systems (see Fig. 1). Without such a system various types of internally and externally generated stimuli, cannot be adequately processed and their features recognized by their origin with respect to the observer.

In some sensory systems, modulation of sensory responses can come from either proprioceptive information or efference copies of the motor command during the preparation for motor output. Efference copies are those neural representations of motor outputs that predict reafferent sensory feedback and modulate the response of the corresponding sensory cortex. Efference copies of the motor command travel to the appropriate sensory cortex preparing it for reafferent stimuli (Cullen, 2004). This system presumably increases the efficiency of attention and cognitive processing by preventing the central nervous system from wasting metabolic resources processing irrelevant sensory stimuli. This process ultimately allows sensory reafferents from motor outputs to be recognized as self-generated and therefore not requiring further sensory or cognitive processing of the feedback they produce (Frith, 1995). Some researchers make minor distinctions between the terms and prefer to use the term corollary discharge (CD) (Sperry, 1950) when discussing signals arising from any stage of motor output that can affect anywhere from the early stages to higher order sensory processing (Crapse & Sommer, 2008a; Sommer & Wurtz, 2002), while the term 'efference copy' (Von Holst & Mittelstaedt, 1950; see review of Cullen (2004)) is used in the same context by others (i.e. Blakemore, Oakley, & Frith, 2003; Ford et al., 2008). In this paper we use the terms interchangeably.

Not only humans are equipped with mechanisms to deal with sensory reafference. Efference copy signals are present across species to prevent allocation of attention to reafference or inhibit maladaptive reflexes. Corollary discharge signals have been studied at

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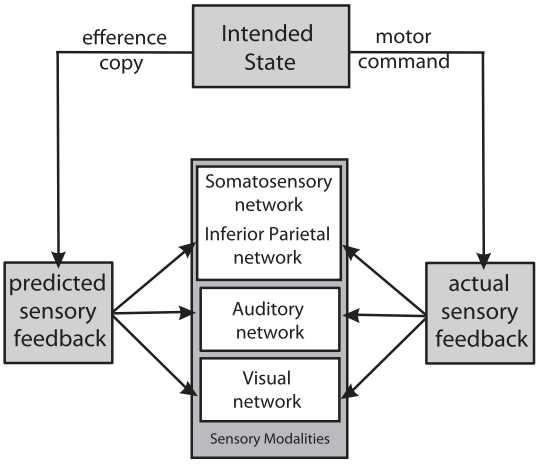

Fig. 1. The efference copy mechanism with sensory feedback to sensory modalities. This mechanism begins with a desired motor command (intended state) sending motor command signals to the motor system for movement execution. This same desired motor command (intended state) sends efference copies to prepare the related sensory modalities (visual, auditory and proprioception/somatosensory) for reafferent feedback.

the cellular level in crickets during chirping behavior. Crickets possess a specific neuron, called the corollary discharge interneuron (CDI), which has widespread connections to several CNS regions, indicating it could affect multiple sensory systems. Recordings from CDI indicate bursts of activity that correspond with sound production during chirping. Paired recordings from CDI and auditory afferent axonal arborizations demonstrate that spikes in CDI result in primary afferent depolarizations that cause presynaptic inhibition in auditory areas (Poulet & Hedwig, 2006). A similar signal has been observed in cockroaches, in giant fibers of the ventral nerve cord during leg movements (Delcomyn, 1977). Cockroaches normally display a running reflex in response to air puff stimuli, yet these extremely sensitive receptors are not activated by the air current generated during movement. This provides evidence at the cellular level that supports the necessity of discriminating between self-induced versus externally induced stimuli across species. This particular example represents a simple inhibition of the sensory and reflex response (which can be categorized as lower-order CD), whereas the effects of CD in many of the primate sensory systems that we will discuss is used by the CNS for more complex sensory analysis (higher-order CD) (Crapse & Sommer, 2008a). For instance, the auditory system in primates is hypothesized to monitor any potential mismatch to expected reafferents with increased sensitivity rather than presenting with an overall attenuated response to noise (Crapse & Sommer, 2008b; Eliades & Wang, 2008).

In both human and non-human primates, research has suggested efference copies have a role in a variety of modulatory functions according to the requirements of each of the sensory networks (Fig. 1). Within the visual system the constantly shifting image on the retina that results from eye, head or body movements must be accounted for when processing the visual image so that these movements do not cause illusory shifting the external environment (Haarmeier et al., 1997). Within the somatosensory system, the corollary discharge signal may inform somatosensory network when tactile stimulation is self-induced (Blakemore, Wolpert, & Frith, 2002). In the auditory cortex, the attenuated response to the sound of one's voice as compared with externally produced auditory stimuli is likely the result of corollary discharge signals (Ford & Mathalon, 2005).

Failures of the efference copy system to generate corollary discharge, or the failure of other CNS areas to receive and integrate these signals has been proposed as a possible cause for symptoms commonly experienced by schizophrenia patients such as auditory hallucinations and delusions of passivity (Blakemore, Wolpert, & Frith, 2000; Blakemore et al., 2002; Feinberg, 1978; Ford & Mathalon, 2004, 2005; Frith, 1995). The inability to predict the sensory consequences of one's actions may result in the subjective experience of being under the control of external forces. Similarly, the failure to recognize one's voice or inner speech as self-generated might produce the subjective experience of an externally generated sound then interpreted as hearing voices. The following sections will review the literature on CD signals in vision, audition and somatosensation and their relation to symptoms experienced by patients with schizophrenia.

2. Efference copies in the visual system

Efference copies in the visual system ensure visual stability in spite of the displacement of the image on the retina during movements – for instance when watching a video taken with an unstabilized camera it is difficult to focus on the images in the scene, however our own movements resulting in the same visual perturbations as we make eye movements or walk down the street are never perceived. The idea that the brain informs and modulates the activity of sensory processing systems of eye position via an efference copy of the motor command was widely disseminated by Herman von Helmholtz and first demonstrated by von Graefe (1854) (Helmholtz, 1924; for review see Cullen, 2004). Eye position modulation has been found in multiple brain regions using a variety of techniques in animals (Andersen, Essick, & Siegel, 1985; Ferraina et al., 2001; Balan and Ferrera, 2003) and more recently in human neuroimaging studies, (Baker, Donoghue, & Sanes, 1999; DeSouza et al., 2000; DeSouza, Dukelow, & Vilis, 2002) indicating that information about eye position is likely important for many of sensorimotor and cognitive processes.

Although it has also been proposed that information about eye position with respect to the head and body comes from proprioceptors in the eye muscles (for more on this topic see Donaldson, 2000; Steinbach, 1987; Wang et al., 2007), it is widely accepted that corollary discharge for saccades provides the accurate information regarding eye position that is necessary for the ability to estimate correct saccade end-points (Guthrie, Porter, & Sparks, 1983; Sommer & Wurtz, 2004a, 2004b see reviews Sommer & Wurtz, 2006, 2008a, 2008b; Wurtz, 2008), and that proprioceptive information about eye position does not reach the cortex fast enough for the online processing of visual space (Wang et al., 2007; Sommer & Wurtz, 2008a; Xu et al., 2011). While many studies provide indirect evidence for a corollary discharge signal, Sommer and Wurtz have conclusively demonstrated a corollary discharge pathway for visual information that sends information pertaining to saccade direction from the superior colliculus through the MD (dorsal medial nucleus of the thalamus) in order to update the receptive fields in FEF (see Fig. 2A). Orthodromic activation of MD activates FEF, antidromic activation of these same neurons activates SC while antidromic activations of FEF activated MD (Sommer & Wurtz, 2004a, 2004b, 2006; Sommer & Wurtz, 2008b). Disruptions of the SC-MD-FEF pathway via muscimol injection to the MD results in inaccurate second saccade endpoints in double step saccades, in which the corollary discharge signal relaying information regarding the position of the eyes after the first saccade is necessary in order to accurately make the second saccade. Corroborating evidence is found in patients with thalamic lesions who also show deficits in making the successive eye movements required for double-step saccades (Bellebaum et al., 2005; Ostendorf, Liebermann, & Ploner, 2010). This corollary discharge signal allows neurons in FEF to update their receptive field

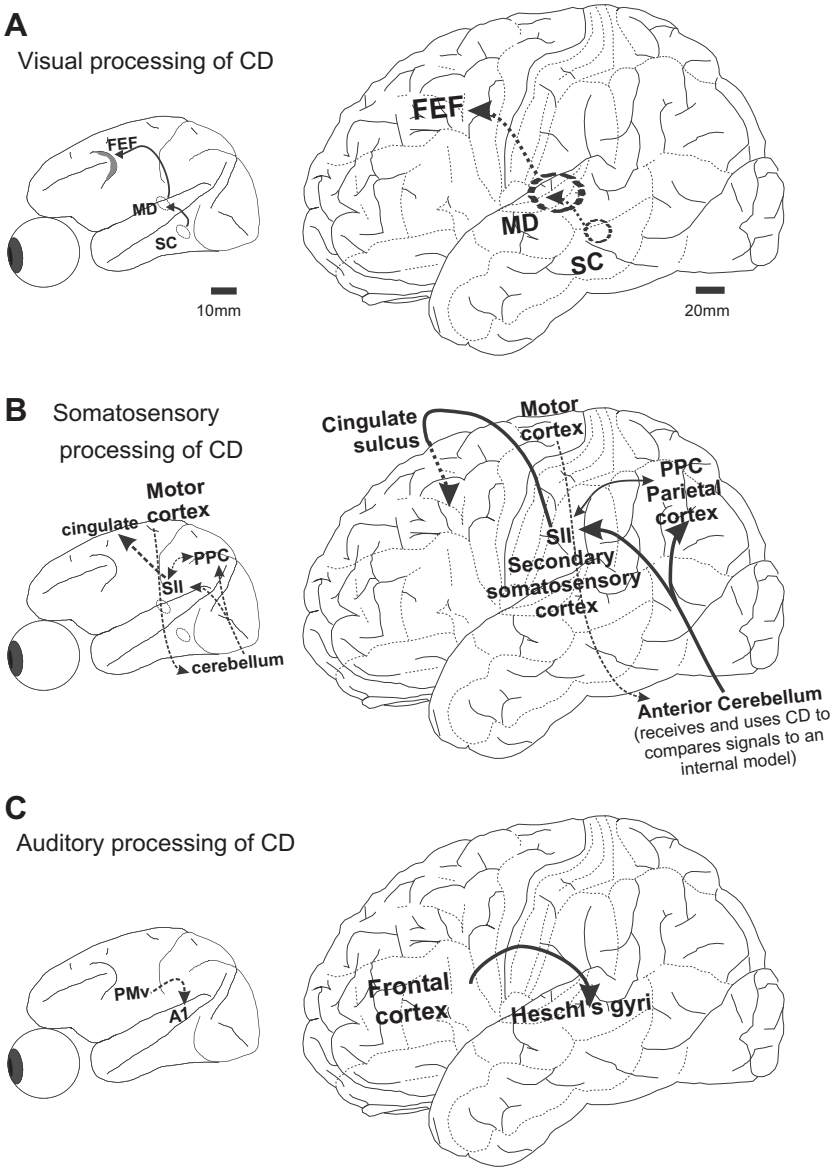

Fig. 2. Three putative efference copy pathways involved in sensory processing from the literature on human and non-human primate studies. Dashed lines are predicted connections and pathways potentially used for CD. Abbreviations: FEF – frontal eye fields; SC – superior colliculus; MD – medial dorsal nucleus of the thalamus; SII – secondary somatosensory cortex.

to the new target location *before* the execution of a saccade. Area LIP, which is primarily involved in selecting saccades towards salient stimuli and is directly connected to FEF, also shares this characteristic presaccadic spatial updating indicating the use of a corollary discharge signal (Duhamel, Colby, & Goldberg, 1992). Information regarding eye position, via a corollary discharge signal, combined with head and body-centered frames of reference not only contribute to spatial updating and the ability to make accurate saccades, they also contribute to visual stability by differentiating between self-generated and externally generated visual changes. Bilateral parieto-occipital lesions, particularly damage to area MST, is believed to be the cause of one patient's false perception of motion during smooth pursuit eye movements and also vertigo-like symptoms due to an inability to compensate for retinal slip (Haarmeier et al., 1997). It has been suggested that CD signals are modified throughout the visual sensorimotor pathway based on the anatomical and functional constraints of each particular structure (Sommer & Wurtz, 2008a).

3. Efference copies in somatosensation and proprioception

Blakemore, Wolpert, and Frith (2000) propose the concept of efference copies to explain the phenomenon of why we are unable to tickle ourselves even if we are tickled by the touch of others (Claxton, 1975; Weiskrantz, Elliott, & Darlington, 1971). Indirect evidence of the effect of efference copies on the processing of afferent somatosensory information has been shown in human neuroimaging studies. When researchers compared subjects undergoing fMRI scans who made movements that either did or did not result in tactile stimulation of the hand they found no difference in the activation of somatosensory cortex. However, externally produced movements resulting in tactile stimuli showed greater activation in bilateral secondary somatosensory cortex, right anterior cerebellar lobe and anterior cingulate, demonstrating that the signals for the expected, self-produced sensory information is filtered out (Blakemore, Wolpert, & Frith, 1998). Supporting the conceptual role of efference copies in the phenomenon of the

attenuated somatosensory cortex response is the finding that manipulations which change the temporal or spatial properties of the expected stimuli result in an increase perceived degree of tickle sensation (Blakemore, Frith, & Wolpert, 1999). That is, efference copies appear to cause suppressed (or otherwise modulated) cortical responsiveness only when the incoming sensory information matches the expected sensory consequences of the action.

Studies on self-monitoring show that the reduced response to self-induced stimuli might result in subjects' inaccurate judgments of force output. When non-clinical subjects were instructed to monitor the force they felt pressed on a lever and then in turn press the lever using the same amount of force, the amount of force used increased on average 38% each turn (Shergill et al., 2003). This is because participants attempted to gauge the force used based the somatosensory input they received, however this input came from an externally generated force. When pressing the lever themselves they then attempted to replicate the same amount of force based on somatosensory input. The force that is now self-generated and the resulting attenuated somatosensory percept translates to an increased amount of force required to experience the same subjective amount of pressure from pressing the lever.

The anterior cerebellar cortex appears to be a critical step in the corollary discharge pathway. Its correlation with primary and secondary somatosensory cortex activity (Blakemore et al., 1999) and its role in processing anticipated versus unanticipated somatosensory stimuli is well established (Gao et al., 1996). Additionally, the cerebellar cortex receives afferents from the inferior olivary complex which response to unexpected proprioceptive or cutaneous stimuli (Gellman, Gibson, & Houk, 1985).

When expectations of feedback are violated (e.g. incongruency resulting from delayed somatosensory feedback), there is an accompanying increase in the right lateral cerebellar cortex (Blakemore, Frith, & Wolpert, 2001). However, self-produced movements resulting in tactile stimulation as compared with those producing no stimulation, results in decreased cerebellar activity (Blakemore et al., 1999, 2001; see Fig. 2B).

This decrease may be a key part of the mechanism that results in attenuated responses to tactile stimuli. For the somatosensory system, the cerebellum may be making use of an efference copy signal, likely originating from premotor structures, to generate an internal prediction of tactile feedback from motor output (see Fig. 1). When tactile input is congruent with this internal prediction, activity of the cerebellum can modify the response in parietal cortex, possibly via the trans-thalamic pathways (Blakemore et al., 1999, 2001; see Fig. 2B). Hyperactivity in the intraparietal lobule (IPL) is associated with difficulty detecting incongruent proprioceptive feedback (Schnell et al., 2008). Violations of expectations regarding somatosensory and proprioceptive feedback can result in attributions of active movements to external sources (Blakemore et al., 2001; Blakemore, Oakley, & Frith, 2003; Spence et al., 1997).

4. Efference copies in audition

Within the auditory system, it is hypothesized that efference copies work by generating a corollary discharge signal which travels to the auditory cortex in the temporal lobe modulating its activation in response to the sound of one's own voice or other self-initiated auditory stimuli. Data gathered from EEG, fMRI as well as single- and multi-unit recordings from monkeys support this hypothesis (Dierks et al., 1999; Eliades & Wang, 2003; Eliades & Wang, 2005; Eliades & Wang, 2008; Ford et al., 2005; Ford & Mathalon, 2004; Ford & Mathalon, 2005; van Lutterveld, Sommer, & Ford, 2011).

While the auditory cortex of monkeys shows an overall weakly excitatory pattern of activity in response to spontaneous self-vocalizations, this is the net result of neurons that exhibit either suppression (majority) or excitation (Eliades & Wang, 2003). Furthermore, the excitatory or inhibitory modulation of auditory cortex correlates with the variability in the acoustics of the vocalizations (Eliades & Wang, 2005). Similar to the response of auditory cortex in humans to self-generated acoustic stimuli, alterations in the vocal feedback (i.e. expected reafferents) change the coding properties of the neurons (Eliades & Wang, 2008). It has been suggested that the decreased response to self-generated sounds does not represent a generalized overall suppression to auditory stimuli but is represents increased sensitivity to any potential mismatch between expected and actual reafferents (Crapse & Sommer, 2008b; Eliades & Wang, 2008). Although it appears that subcortical structures are key to generating and relaying corollary discharge signals in the visual and somatosensory systems, the origin of suppression likely is not the inferior colliculus (IC), based on both the magnitude of A1 (primary auditory cortex) suppression and the targets of the anatomical efferents for those IC areas which show sensorimotor suppression (Eliades & Wang, 2005; see Fig. 2C).

Research using EEG in humans has revealed that, compared with clinical populations, non-clinical adults show reduced activation of auditory structures as measured by N1, the negative waveform seen in EEG patterns approximately 80–100 ms after onset of the stimulus (originates from auditory cortex bilaterally). EEG assessments of band coherence, a good indication of the functional inter-relationship between two structures, have been used to study corollary discharge in healthy adults. Non-clinical populations show a high degree of band coherence between frontal and temporal lobes during talking (Ford & Mathalon, 2004; Ford & Mathalon, 2005). Band coherence is lowered as recorded sounds or real-time feedback of participants' own voices were distorted (Ford et al., 2005). However, temporal lobe attenuation does not occur solely from the sound of one's own voice. During an MEG study researchers recorded from the supratemporal auditory cortex while participants heard externally produced tones, or heard tones that they elicited themselves with a button-press (Martikainen, Kaneko, & Hari, 2005). N100m waveforms (also approximately 100 ms after stimulus onset) were significantly weaker in the self-produced condition.

Thus, as with efference copies in the somatosensory system, auditory cortical sensory suppression only occurs when the anticipated sensory consequences of self-generated sounds match the actual sensory feedback (see Fig. 2B and C). Results of EEG and MEG research indicate the attenuated response of auditory cortex occurs in non-clinical populations but not with schizophrenia patients (Ford & Mathalon, 2004; Ford & Mathalon, 2005). The pathway for CD appears to originate in frontal areas traveling to auditory cortex, and researchers propose the weaker overall response represents the monitoring by auditory cortex of actual and anticipated sensory feedback (Eliades & Wang, 2005; see Figs. 1 and 2C).

5. Overview of common symptoms in schizophrenia

Schizophrenia is a psychiatric illness that encompasses a wide range of symptoms including psychosis that are typically associated with extensive neurological abnormalities. Positive symptoms, characterized by perceptions and behaviors that should be absent, include experiences such as hallucinations, delusions of persecution and grandeur as well as passivity (where patients feel as though their action are controlled by an external force) and thought insertion (Andreasen & Olsen, 1982). Negative symptoms

encompass the absence of normal behavioral and emotional states such as anhedonia, flattened affect, poverty of speech, avolition and social withdrawal. They are likely present prior to onset as they are associated with poor premorbid functioning (Andreasen et al., 1990) and often precede positive symptoms (Hafner et al., 1993). Related to negative symptoms, cognitive symptoms include difficulties in sustained attention, abstract thinking as well as learning and memory.

Both cognitive and negative symptoms appear to be present to a degree early in disease progression (McGlashan & Fenton, 1992) and retrospective studies suggest they are evident even in early childhood.(Hollis, 1995; Walker et al., 1993; Walker & Lewine, 1990; for review see Ellison, Van Os, & Murray, 1998). Performance deficits on saccade tasks and abnormal scanpaths have been found not only in schizophrenia patients but also their first degree relatives (Beedie, Benson, & St. Clair, 2011; Clementz, McDowell, & Zisook, 1994; Loughland, Williams, & Harris, 2004; Park, Holzman, & Goldman-Rakic, 1995; Raemaekers et al., 2006). These are tasks relying on dorsolateral prefrontal cortex (DLPFC) and intact fronto-striatal pathways that, along with other standardized cognitive tests of frontal lobe functioning, are typically related to the extent of patients' negative symptoms (Clementz, McDowell, & Zisook, 1994; Hammer, Katsanis, & Iacono, 1995; Miller & Cohen, 2001; Winograd-Gurvich et al., 2008; for review see Beedie, Benson, & St. Clair, 2011). These results suggest an association between PFC functioning and negative symptoms. Collectively, PET and fMRI studies suggest a lack of task-dependent frontal activation and overall frontal hypoactivity in schizophrenia patients compared with controls (Barch et al., 2001; Rodriguez et al., 1997; Sanfilipo et al., 2000; Spence et al., 1997; for review Semkovska, Bedard, & Stip, 2001).

The emergence of positive symptoms of schizophrenia are thought to be the result of deficits in self-monitoring due to corollary discharge failure. Without corollary discharge patients are unable to accurately attribute the cause of sensory stimuli as produced by the actions of themselves versus the actions of others or changes in the environment (Blakemore, Wolpert, & Frith, 2002; Fletcher & Frith, 2009; Frith, Blakemore, & Wolpert, 2000; Jeannerod, 2009). We will further explore the possibility that anatomically distributed brain areas are lacking the tighter functional connection found in most non-clinical populations, not only disrupting efficient cognitive processing but preventing communication between cortical regions necessary for the proper transmission of corollary discharge signals.

6. Evidence for efference copy failure in schizophrenia

Many patients experiencing symptoms of passivity do not feel that their actions and thoughts are discrepant with their intentions, but merely feel beyond their own control, thus congruent with the hypothesis of efference copy failure (Blakemore, Wolpert, & Frith, 2002; Frith, Blakemore, & Wolpert, 2000). Evidence for efference copy failure is closely associated with hallucinations and delusions in both schizophrenia and bipolar patients. In fMRI, the decrease in BOLD response to self-produced tactile stimuli as compared with externally produced tactile stimuli is typically associated with a decrease in subjective feeling of intensity in healthy controls. This decrease in intensity is absent in those patients with positive symptoms (both bipolar and schizophrenia patients) as compared to patients without positive symptoms and non-psychiatric controls (Blakemore et al., 2000). This shows the association between the class of symptoms and indicators of efference copy failure. Current data on the neural substrates of hallucinations support the notion that they are indeed processed and perceived as real stimuli in the external environment, recruiting primary sensory processing areas such as Heschl's gyrus in patients experiencing auditory hallucinations (Dierks et al., 1999; Oertel et al., 2007).

Indicators of self-monitoring failures in neuroimaging and on behavioral tasks have been found across a variety of sensory systems. For instance, the previously discussed paradigm where non-psychiatric subjects attempted to replicate the amount of force used while pressing on a lever actually increased with each turn indicating a dampened perception of self-induced somatosensory stimulation was replicated with schizophrenia patients. Consistent with the hypothesis of efference copy failure or deficits in self-monitoring, patients with schizophrenia experience less attenuation due to self-generated forces and were more accurate at mimicking externally generated force used than were controls (Shergill et al., 2005).

When monitoring visual reafference, research suggests deficits in identifying delayed visual feedback are attributed to a dysfunctional comparator mechanism. In non-clinical populations any incongruence between the visual feedback of the motor sequence and the execution of that motor sequence caused an increased activation in bilateral putamen and medial thalamus as well as activation on the border of the left MT/supramarginal gyrus that positively correlated with the delay (implying this system is monitoring expected feedback from motor output). Schizophrenia patients, however, do not appear to have any brain regions accurately monitoring congruence of this feedback (Leube et al., 2010).

This dysfunction in predictive motor abilities is accompanied by greater variability of their internal predictions of the sensory consequences of self-action than non-clinical groups and it is suggested that this may contribute to their inability to accurately identify distortions in the sensory consequences (i.e. visual feedback) of motor output. The increased variability in internal predictions positively correlated with patients' scores in clinical assessments of their positive symptoms. This is accompanied by a higher threshold for detecting spatially incongruent visual feedback, and the authors suggest this deficit may be directly related to the highly variable and therefore more unreliable predictions of visuo-motor feedback (Synofzik et al., 2010). While it appears non-clinical adults make use of CD signals in the visual system to ensure visual stability across smooth pursuit eye movements (Haarmeier et al., 1997), manipulation of stimuli during smooth pursuit results in perception of movement of the environment more readily in schizophrenia patients than control subjects, suggesting there may be disturbances in this system (Lindner et al., 2005). Additionally, schizophrenia patients have a higher threshold for detecting motion in visual stimuli (Wertheim et al., 1985). Abnormal smooth and predictive pursuit eye movements have also been noted and deficits in predictive measures have been attributed to a failure to integrate corollary discharge signals with pursuit responses (Thaker et al., 1999).

Neuroimaging results link symptoms of passivity with increased parietal activation that fails to show stimulus-driven modulation. Regarding symptoms of passivity, patients with schizophrenia show a general hypofrontality and activation of the right inferior parietal lobule compared with normal control subjects (Gur et al., 1998; Spence et al., 1997) that the authors interpret as a failure of efference copy signals. Differences in parietal activation compared with controls supports the hypothesis that increased noise in the parietal-cerebellar network results in a failure to monitor the patients' actions and attribute the cause to self-movement (Blakemore, Oakley, & Frith, 2003; Schnell et al., 2008).

7. Functional and anatomical abnormalities in schizophrenia

Research into the pathophysiology of schizophrenia using post-mortem patients and techniques such as PET and MRI has lead to

many discoveries of aberrant structural development in multiple neural areas, collectively these methods point to cortical grey matter and white matter deficits as well as thalamic abnormalities. Structural and functional abnormalities within the three major sensory systems previously discussed are associated not only with the occurrence and severity of positive symptoms, but also with cerebral atrophy and negative or cognitive symptoms. Even where the issue of hypofrontality is unclear, prefrontal dysconnectivity appears as a robust finding and is associated with both positive and negative symptoms.

Within the visual system, a reduction in size and glucose metabolism of thalamic MD in schizophrenia patients (Buchsbaum et al., 1996; Byne et al., 2001; Hulshoff Pol et al., 2001; Kemether et al., 2003), could be perturbing the critical CD pathway (Sommer & Wurtz, 2004a; Bellebaum et al., 2005; Ostendorf, Liebermann, & Ploner, 2010), thus inhibiting the process of spatial updating. This may represent at least part of the neural basis for predictive pursuit deficits, high thresholds for motion perception and reduced background motion necessary for rendering an image perceptually stable during eye movements (Lindner et al., 2005; Thaker et al., 1999; Wertheim et al., 1985).

Within the auditory system, research has found grey matter volume reductions in the brains of schizophrenia patients bilaterally in superior temporal gyrus (STG) and prefrontal white matter reductions correlated with the severity of negative symptoms (Sanfilipo et al., 2000). The severity of auditory hallucinations is correlated with the extent of temporal lobe degeneration, specifically the left superior temporal gyrus (Barta et al., 1990; Levitan, Ward, & Catts, 1999), as well as the degree of frontotemporal functional (Lawrie et al., 2002; Mechelli et al., 2007; Rotarska-Jagiela et al., 2010) and anatomical connectivity (Rotarska-Jagiela et al., 2009; Shergill et al., 2007).

It has been suggested that higher motion detection thresholds could be due to greater noise in the vestibular system, resulting in greater noise in the reference signal making a stimulus appear to be moving slower than it actually is (Wertheim et al., 1985). This is consistent with the findings showing increased variability in patient's estimation of visual congruence with their own proprioceptive signals. The results indicating hyperactivity in parietal cortex also support the hypothesis that schizophrenia patients experience increased noise in sensory systems and this is associated not only with feelings of passivity, but also hypofrontality (Spence et al., 1997).

Hypofrontality, both at rest and during cognitive tasks, as well as poor task performance is a commonly reported finding among schizophrenia patients (Barch et al., 2001; Menon et al., 2001; Spence et al., 1997). Although these findings are somewhat equivocal (Manoach, 2003), studies that were able to elicit task-dependent activity on par with controls failed to show the concomitant decrease in activity in those areas implicated in positive symptoms, namely parietal cortex and superior temporal gyrus, that is found during prefrontally mediated tasks in control subjects. This implies that while regional specialization in areas such as DLPFC *might* be disrupted, it is likely related to broader deficits in functional integration across cortical areas. The results of frontotemporal and fronto-parietal dysconnectivity have been found using prefrontally mediated tasks, both with normal DLPFC activation as well as hypoactivation, but most importantly they have been found in patients with both negative and positive symptoms (Allen, Liddle, & Frith, 1993; Crossley et al., 2009; Fletcher, McKenna, Friston, Frith & Dolan, 1999; Friston et al., 1991; Frith, 1995; Lawrie et al., 2002), including those with auditory hallucinations and no impairments in verbal fluency. Additionally, patients with passivity symptoms and hyperactivity in parietal cortex also appear hypofrontal, and to a greater degree when most symptomatic (Allen, Liddle, & Frith, 1993; Frith, 1995; Fletcher et al., 1999; Spence et al., 1997). Thus, findings linking PFC activation and task performance with negative or cognitive symptoms may not be clearly dissociated from those results thought to be related to positive symptoms and failures of internal monitoring.

These findings suggesting abnormalities in cortical and thalamic structures as well as regional hypo- and hyper-metabolism may ultimately represent compromised connectivity between sensorimotor regions that is otherwise key for predictions of sensory reafferents (Fletcher & Frith, 2009). Thus, some researchers have hypothesized that hypofrontality and the associated cognitive deficits may be related to functional dysconnectivity, which appears to play a role in internal monitoring and consequently the neural basis of positive symptoms as well. When frontal regions fail to inhibit, or otherwise modulate, temporal and parietal cortex due to a lack of normal functional pathways, this results in auditory hallucinations and delusions of alien control (Spence et al., 1997; Weinberger & Berman, 1988).

8. Trans-thalamic pathways in functional integration and self-monitoring

It is possible that abnormalities in cortical functioning have origins in thalamic dysregulation. The thalamic reticular nucleus (TRN) is a band of exclusively GABA-erigc neurons through which all cortico-thalamic (CT) and thalamo-cortical (TC) projections must pass, including afferents from prefrontal cortex and topographically organized sensory information (McAlonan & Brown, 2002; McAlonan, Cavanaugh, & Wurtz, 2008; Zikopoulos & Barbas, 2006). TRN controls responses to afferent sensory information in both primary sensory cortices and thalamic nuclei, and lesions to this area result in attentional deficits (Krause, Hoffmann, & Hajos, 2003; McAlonan, Cavanaugh, & Wurtz, 2008; Skinner & Yingling, 1977; Villa, 1990). Synchronizing of thalamo-cortical rhythms and integrating both top-down (attentional) and bottom-up (sensory) information, it plays a crucial role in the processes that underlie conscious perceptual experience (Behrendt, 2006).

One of the mechanisms to achieve this involves controlling the switch of thalamocortical cells between tonic and burst firing mode. In animal models burst firing mode, whereby neurons fire groups of action potentials rapidly in sequence, appears to increase the salience of relevant sensory stimuli, and adapt the processing of sensory information according to context, i.e. sensory processing and the internal monitoring of actions (Krause, Hoffmann, & Hajos, 2003; review, Vukadinovic & Rosenzweig, 2012). Sustained hyperpolarization is required for neurons to switch to burst firing mode, and schizophrenia is associated with a genetic predisposition for a lack of slow-deactivating potassium channels (Huffaker et al., 2009) As Vukadinovic and Rosenzweig (2012) note, this could lead to increased excitability rather than hyperpolarization and reduced ability to switch to burst firing mode. This is consistent with both the dopamine hypothesis and the NMDA hypofunction model of schizophrenia and animal models of schizophrenia show an increase in burst firing mode with the administration of haloperidol (Krause, Hoffmann, & Hajos, 2003). Indirect evidence of TRN dysfunction in adult schizophrenia is present in the form of reduced sleep spindle activity. Sleep spindles are generated by the TRN and their reduction is correlated with the severity of positive symptoms and is unrelated neuroleptic medication (Ferrarelli et al., 2007; Ferrarelli et al., 2010).

In addition to controlling ongoing sensory and cognitive processes in adulthood, it also plays an important role guiding axons in cortico-cortical and cortical-thalamic connections during embryonic development (Deng & Elberger, 2003; Ulfig, Nickel, & Bohl, 1998; Villa, 1990) and it has also been suggested to be a structure particularly sensitive to ischemia during peri-natal

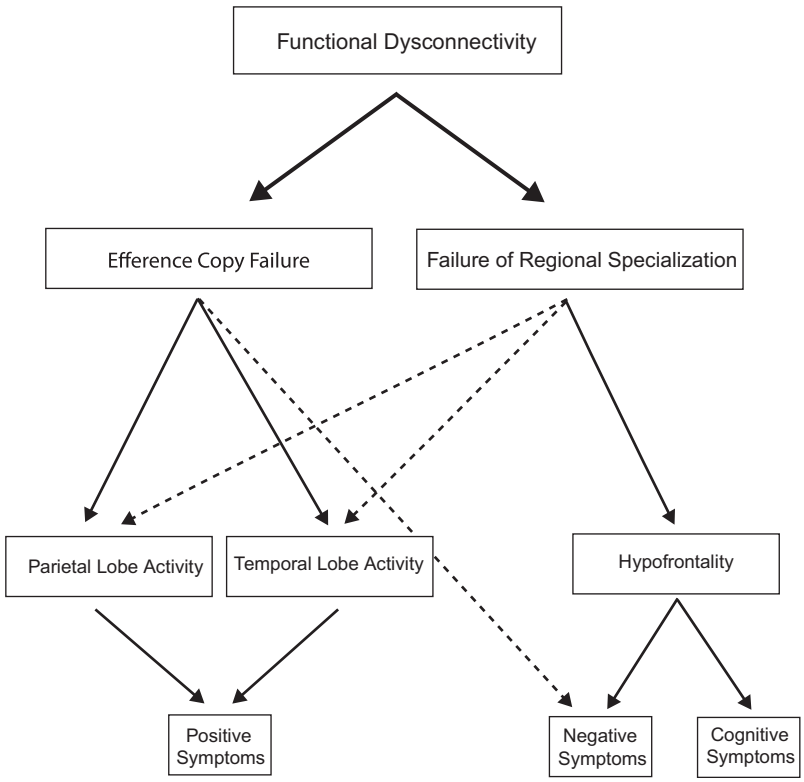

Fig. 3. Hypothetical path diagram showing the flow of disruptions in brain functioning due to the failure to establish strong synaptic connections between brain regions. *Functional Dysconnectivity* – manifest in brain imaging studies as uncorrelated activity between distributed brain regions. *Efference copy failure* – without distributed brain regions effectively interacting, motor signals no longer modulate sensory cortices. *Regional Specialization* – functional dysconnectivity limits afferents required for the formation of localized, functionally specific areas. *Hypofrontality* – Prefrontal hypometabolism, often viewed as a primary deficit in schizophrenia patients, may be secondary consequence of disconnectivity. *Temporal and Parietal Lobe Activity* – evidence for efference copy failure from neuroimaging shows patients with abnormal activity in parietal and temporal uncorrelated with task performance or activity in other cortical areas. Dashed arrows indicate the possibility of disrupted local development in addition to abnormal afferent connections. *Negative and Cognitive Symptoms* – associated with patient deficits in prefrontal functioning. First degree relatives also show defits on some frontal lobe tasks, perhaps sharing some degree of dysconnectivity and subsequent hypofrontality. Dashed arrow represents the hypothesized role of efference copy failure in negative symptoms where unpredictable sensory signals make actions seem inconsequential. *Positive Symptoms* – Delusions of passivity and auditory hallucinations have both been associated with abnormal activity in parietal and temporal lobes, unmodulated by other brain areas.

periods (Ross & Graham, 1993). Thus peri-natal complications, occurring at elevated rates among these patients (Cannon, Jones, & Murray, 2002), could potentially perturb its functioning and disrupt axonal guidance during the formation of cortical connections (Ulfig, Nickel, & Bohl, 1998).

Converging evidence suggests increased excitability of TRN neurons in schizophrenia patient populations. Given its anatomical functional properties, if TRN is an early and persistent disruptor of cortical development, local processes in specific regions (i.e. prefrontal dysregulation) and the functional integration of specialized areas (i.e. fronto-temporal dysconnectivity) could be affected as well as short-term processes such as the ability to switch between tonic and burst firing mode. The impact of this dysfunction on schizophrenia symptoms is illustrated in our hypothetical diagram in Fig. 3.

9. Conclusion

Evidence for corollary discharge (CD) at the cellular level demonstrates that a mechanism accounting for internally generated sensory reafferents is a necessity even for simple behaviors, such as those in crickets and cockroaches, in order to prevent the maladaptive use of reflexes as well as the processing of redundant stimuli. As the organisms and behaviors increase in complexity and flexibility of behavior, corollary discharge signals become a heterogeneous set of neural signals that occur in pathways spanning multiple brain regions. A simple structure in invertebrates, such as the corollary discharge interneuron in crickets that attenuates the auditory response to self-generated chirping, may have many functionally homologous pathways in the human brain. These include the robust fronto-temporal connections which may be responsible for attenuated auditory response to self generated sounds, the fronto-parietal and cerebellar–parietal connections that might tell us somatosensory or proprioceptive feedback is result of self-generated movement, or the medio-dorsal nucleus of the thalamus connecting superior colliculus with frontal eye fields allowing for presaccadic spatial updating. Efference copy structures and pathways, whether simple or complex, are necessary to evaluate sensory information and separate what is self-generated from more relevant stimuli within the environment. There are diffuse structural and functional abnormalities seen in schizophrenia that encompass many of the regions that have been suggested to play a role in generating, sending, or receiving corollary discharge signals. These include parietal cortex, thalamic nuclei, prefrontal and temporal areas and their distributed patterns of activity. Results from behavioral data comparing the experience of self-generated versus externally-generated input provide additional evidence that patients have deficits in this type of discrimination and it is possible that the consequences are some of the puzzling and complex symptoms covered in this paper.

Although there is ample evidence for self-monitoring deficits in schizophrenia patients, there is little research incorporating what is known about CD failure or the lack of functional connectivity between brain areas with hyperactivity of dopamine pathways,

which currently represent the major avenue of treatment for schizophrenia patients. It seems that while CD failure is informative with regard to sensory and cognitive processing in patients, it has limited prescriptive capability. Furthermore, while research shows that sensory prediction deficits often correlate with the degree to which patients experience positive symptoms, the theory offers no explanation for the content of auditory hallucinations or symptoms of passivity experienced as being under the control of specific agents. It also contributes little to what is known about the etiology of schizophrenia with respect to the interaction between environmental stressors and genetic vulnerability. To what degree do sensory prediction deficits result in psychopathology? Are they predictive of psychosocial outcome? More research elucidating the relationship between patients' deficiencies in self-monitoring, treatment and long-term prognosis is needed.

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