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The relationship between membrane pathology and language disorder in schizophrenia ☆

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Abstract

Receptive language disorder in schizophrenia has been hypothesized to involve a fundamental deficit in the temporal (time-based) dynamics of brain function that includes disruptions to patterns of activation and synchronization. In this paper, candidate mechanisms and pathways that could account for this basic deficit are discussed. Parallels are identified between the patterns of language dysfunction observed for schizophrenia and dyslexia, two separate clinical disorders that may share a common abnormality in cell membrane phospholipids. A heuristic is proposed which details a trajectory involving an interaction of brain fatty acids and second-messenger function that modulates synaptic efficacy, and, in turn, influences language processing in schizophrenia patients. It is additionally hypothesized that a primary deficit of functional excitation originating in the cerebellum, in combination with a compensatory decrease of functional inhibition in the prefrontal cortex, influences receptive language dysfunction in schizophrenia.

Keywords: Schizophrenia; Receptive language disorder; Membrane pathology

1. Introduction

Schizophrenia is a severe, chronic psychiatric disorder that affects approximately 1% of the population, and involves significant cognitive dysfunction, including language disturbances [1]. Receptive language dysfunction in schizophrenia patients is well documented, although the pathophysiology of these diagnostic features has not been determined. One proposal involves a relationship between schizophrenia and dyslexia based on a common abnormality in cell membrane phospholipids [2]. Schizophrenia and dyslexia are separate clinical disorders, but, in fact, independent lines of evidence are suggestive of parallels between their hallmark features, characteristic cognitive dysfunction, and potential pathophysiology. Traditionally, dyslexia was defined as a reading disorder that exists within the context of adequate motivation, intelligence, and educational opportunity [3]; recent discussions include recognition of additional cognitive dysfunction [4–8], such as working memory deficits [9], and symptoms of schizotypal personality disorder [10]. In the most recent Diagnostic and Statistical Manual of Mental Disorders [1], the symptoms of schizophrenia include but are not limited to language disturbance.

2. Receptive language dysfunction in schizophrenia

Disturbances in two broad categories of receptive language function characterize schizophrenia patients and their first-degree family members: semantic (word meaning) processing, indexed by semantic priming deficits, and language comprehension, including syntactic relations ('who did what to whom?'). Performance decrements in these two domains have been consistently observed across samples and laboratories, including: single-word perception at variable levels of intensity [11] and background noise [12]; behavioral and electrophy-

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Table 1
Proportion of schizophrenia patients and their non-psychotic first-degree family members exhibiting abnormal performance ($\geqslant 1$ SD for normal controls) during receptive language processing

	n (% of sample)
Schizophrenia patients	
Single-word processes—N400 Priming effect[a]	
Medicated patients ($n = 30$)	12 (40)
Unmedicated patients ($n = 21$)	10 (48)
Syntactic relations—response accuracy ($n = 32$)[b]	18 (32)
Non-psychotic first-degree family members	
Single-word processes	
WRAT-3 reading ($n = 39$)	19 (49)
WRAT-3 spelling ($n = 39$)	17 (44)
Syntactic relations—response accuracy ($n = 30$)	10 (33)

[a] See Ref. [27].
[b] See Ref. [23].

siological (event-related brain potentials) responding to single-word (semantic priming deficits: for a review, see Ref. [13]) and sentential [14–17,19] contexts; and response accuracy and latency for information and syntactic relations in sentences [20–25]. Moreover, receptive language dysfunction during early childhood has been observed in individuals who later developed schizophreniform disorder during early adulthood [26]. This latter finding suggests that receptive language dysfunction predates a schizophrenia diagnosis in adulthood, and implies a neurodevelopmental process for this cognitive dysfunction. Finally, as shown in Table 1, a substantial proportion of patients and their first-degree family members show abnormal performance ($\geqslant -1$ SD for control groups) across a variety of receptive language processing tasks, including single-word reading and spelling, activation of semantic memory during word/non-word discrimination, and syntactic relations. The collective findings clearly indicate that the functional integrity of the language system is compromised in schizophrenia, although the key brain regions and cellular mechanisms responsible for this dysfunction remain to be determined.

Receptive language disturbance in schizophrenia may be caused by a fundamental deficit in the temporal (time-based) dynamics of brain function that includes disruptions to patterns of activation and synchronization. We previously proposed that language disturbance in schizophrenia is due to compromises in two basic cognitive functions: processing of rapid, sequential stimuli; and binding or functional connectivity of processes occurring in distributed brain regions [28,29]. It is not known if these basic functions are independent or correlated. However, a primary or core deficit in the temporal dynamics of brain function could cause both disturbances by disrupting patterns of activation and synchronization. In this paper, it is suggested that abnormalities in cell membrane function may affect both types of disruption. To our knowledge, there is no direct evidence for the hypothesized relationship between phospholipid abnormalities and language dysfunction in schizophrenia. Our goal is to describe tentative hypotheses that are necessarily speculative and provide indirect links between empirical findings and possible mechanisms. We first summarize our hypotheses about the possible causes of receptive language dysfunction in schizophrenia, and then discuss possible links between these deficits and abnormalities in cell membrane phospholipids.

2.1. Deficit in the processing of rapid, sequential stimuli

Language processing is rate dependent. The optimal rate for reading prose is estimated to be ~ 300 words per min (5 words/s), with systematic declines in understanding accuracy occurring beyond that rate [30]. Timing parameters influence single-word processing, with stimulus duration and presentation rate both affecting level and distribution of brain activation in healthy individuals [31–33]. Disturbances in time-dependent processes may be fundamental to schizophrenia disorder. Robust performance deficits have been observed for schizophrenia patients during their perception of rapid, sequential bits (e.g., letters) of visual and auditory information [34]. Visual masking and auditory gating tasks have typically been used by cognitive researchers to limit the amount of time that a stimulus can be processed. In the standard visual backward masking paradigm, for example, two stimuli are presented sequentially (target-mask sequence); the first stimulus (letter) is followed in quick succession by the second stimulus (pattern mask) and the subject's task is to identify the first stimulus (letter). At short inter-stimulus intervals, healthy individuals have difficulty in correctly identifying the target; schizophrenia patients show an increased disadvantage on this task [35–41].

The pattern of results obtained for the visual backward masking paradigm suggests that temporal processing deficit in schizophrenia may not involve a generalized slowing phenomenon, in that patients' performance does not show a strong linear relationship between presentation rate and accuracy. Braff and colleagues [34] argued that refined distinctions based on neural pathways and channel functions will likely be necessary to account for temporal processing disturbance in schizophrenia, and the transient/sustained neural channel model of Breitmeyer and colleagues [42,43] was offered as a heuristic. This model is based on the parallel and complementary pathways of the visual system, in particular, the lateral geniculate nucleus of the thalamus, with functional distinctions based on the temporal frequency and spatial resolution of stimuli.

Transient-channel (magnocellular) function is biased toward stimuli of high temporal frequency (rapid presentation rate) and low spatial resolution (widely spaced/low-density pattern); whereas sustained-channel (parvocellular) function is biased toward stimuli of low temporal frequency (slow presentation rate) and high spatial resolution (closely spaced/high-density pattern) [44,45]. Extending this model to schizophrenia, Green and colleagues [40] proposed that patients' visual backward masking deficit is due to an over-reactive transient channel (magnocellular) response to the rapid mask that interferes with the sustained channel (parvocellular) response to the target. In parallel, deficits in time-dependent processing may also be integral to dyslexia [46–48], and a magnocellular deficit theory has also been advanced for this disorder [49,50]. Supportive evidence includes postmortem tissue abnormalities (small cell bodies and disorganized architecture) identified in the magnocellular pathway of the lateral geniculate nuclei from individuals with dyslexia; in contrast, abnormalities were not observed in dyslexics' parvocellular layers [51].

To our knowledge, the visual backward masking paradigm has not yet been extended to single- and multiple-word processing in schizophrenia patients. Semantic memory function, however, may also be influenced by the mechanisms proposed to explain patients' visual backward masking deficit. Time-based processes are a prominent feature of cognitive theories of semantic memory. Most cognitive models include some version of a semantic network in which words are represented as either independent [18,52] or distributed [53] units. Links or pathways are assumed to interconnect these units throughout the semantic network. Access to and within this network has been traditionally viewed as involving two broadly distinguishable cognitive mechanisms; automatic or spreading activation and controlled processing [54,55]. In general, automatic activation is assumed to occur rapidly, without variation in pattern, and, in some theories, without capacity limits. Controlled attention is assumed to be conscious, intentional, and capacity limited. Automatic activation is therefore expected to be prominent under rapid presentation rates (<500 ms stimulus onset asynchrony); controlled attention is believed to emerge under comparatively longer presentation rates ($\geqslant 500$ ms stimulus onset asynchrony). Controlled processing is known to influence semantic memory in schizophrenia. In contrast, findings have been equivocal regarding the influence of automatic activation on semantic processes in schizophrenia [13], with some data supporting intact automatic activation and other data indicating either below normal or supra-normal operation of this mechanism. These inconsistencies are likely due to a combination of factors, including: the wide range of timing parameters (stimulus duration, presentation rate) employed across studies; and the collective findings for healthy individuals [31–33] showing that even subtle differences in timing parameters influence level and distribution of brain activation produced by single-word processing. Priming studies in which similar timing parameters (350 ms stimulus onset asynchrony) were employed have revealed abnormal automatic activation in schizophrenia patients, as indexed by electrophysiological (event-related brain potential) responding [56,57]. It is not presently known if semantic (word meaning) processing deficits in schizophrenia may be due to disturbance of sub-cortical circuitry, such as magnocellular pathway-transient channel dysfunction. Findings of structural and cytoarchitectural abnormalities in the thalami of schizophrenia patients (decreased numbers and density of neurons; reduced synaptic protein rab3a) [58] lend plausibility to the hypothesis that thalamic pathways are involved in some aspects of cognitive dysfunction in schizophrenia patients. This possibility requires empirical evaluation.

Timing functions possibly governed by the cerebellum provide an additional candidate mechanism and brain circuitry for disturbances in the processing of sequential, rapid stimuli for schizophrenia patients. Traditionally, the cerebellum has been associated with control and coordination of movement [59], and motor dysfunction (voluntary and involuntary movement) has been carefully described for both schizophrenia patients and individuals at biological risk for the disorder [60]. Findings from recent studies, however, indicate additional functional roles may be served by this brain region, including cognition (working memory) and language [61]. Of relevance for the present focus, the integrity of cerebellum morphology appears to be important for time-based processing. Patients with cerebellar lesions, compared to various neurological controls (Parkinson's disease, pre-motor cortical lesions, healthy), showed deficient performance on perceptual tasks requiring fine discriminations of stimulus duration, timing, and velocity [62,63], but not stimulus position [62]. Moreover, case study data have revealed a dissociation of perceptual and motor functions, and lesions in lateral and medial cerebellum; lateral cerebellar lesions were associated with perceptual timing functions, and medial lesions were associated with motor performance [64]. Cerebellar pathways also appear to be involved in the temporal processing of linguistic stimuli. Price and colleagues [31,32] found that exposure duration (150 and 1000 ms) and presentation rate (20–120 words per min) for visual language stimuli produced different patterns of regional cerebral blood flow (rCBF) in the cerebella of healthy individuals. The strongest activation in this brain region was produced by short duration stimuli presented at the fastest rates. Thus, the combined influence of stimulus duration and presentation rate has been shown to modulate the level

and pattern of brain activation in the cerebella of healthy individuals, which has implications for clinical populations characterized by disturbances in the processing of rapid, sequential information.

Structural and functional alterations in cerebellar circuitry have been observed both for schizophrenia patients [58,65] and for individuals with dyslexia [48,66]. Andreasen and colleagues [67] found that schizophrenia patients, compared to healthy controls, were characterized by decreased cerebral blood flow during both novel and well-learned narrative recall tasks. Group differences in activation were observed in cerebellar, thalamic, and frontal regions. An important aspect of the Andreasen et al. finding is that patients' cerebral blood flow in these pathways was significantly reduced for the well-learned task even though their behavioral accuracy did not differ from that of controls. Temple and colleagues [48] found that brain activation (fMRI) to rapid, non-linguistic acoustic stimuli differed between individuals with dyslexia and non-dyslexic controls. The primary distinction between the two groups involved controls' increased activation in left prefrontal cortex (PFC) for rapid stimuli; this pattern was absent in the dyslexia group. Of importance to the present discussion, dyslexics also differed from controls in their activation of right posterior cerebellum. The interpretation of this latter effect is not straightforward; dyslexics showed increased cerebellar activation for slow stimuli compared to rapid stimuli, while controls exhibited the reverse pattern.

The structural integrity of cerebellar pathways has not been well studied for schizophrenia. The available evidence is suggestive of alterations in the number, size, and structure of Purkinje cells and cells in the dentate nucleus [58,65]. In contrast, hemispheric asymmetry of the cerebellum has been implicated for dyslexia. Rae and colleagues [66] observed cerebellar asymmetry (right gray matter > left gray matter) for a non-dyslexic control group, but not for the dyslexic group. More importantly, the degree of cerebellar symmetry in the dyslexic group was correlated with their phonological decoding performance (reading time for non-sense words).

In summary, schizophrenia and dyslexia disorders are both characterized by deficits in the processing of rapid, sequential stimuli, which may involve multiple systems including the magnocellular pathway of lateral geniculate nucleus in the thalamus and pathways of the cerebellum.

2.2. Failure of binding or functional connectivity between distributed brain regions

Findings across imaging studies (positron emission tomography, functional magnetic resonance imaging) [68–72] indicate that the brain regions activated during language processing are numerous and widely distributed, including: *single-word reading*—left lateralized regions in occipital and occipito-temporal cortex, left prestriate cortex, left and posterior striate cortex, posterior parietal cortex, superior and middle temporal cortex, left frontal operculum, medial regions in supplementary motor area and anterior cingulate, primary motor cortex, and bilateral regions in cerebellum; *sentence processing*—left perisylvian cortex, left inferior-frontal gyrus including Broca's area, angular and supramarginal gyri. Furthermore, syntactic complexity of sentence structure and word frequency of sentence constituents jointly influence brain activation in a number of regions, including: left inferior frontal cortex (Broca's area), left superior and middle temporal regions (Wernicke's area), left inferior parietal cortex (angular and supramarginal gyri), and left dorsolateral PFC [70]. Functional connectivity of activation in spatially distributed brain regions therefore appears critical for optimal language processing.

Dopaminergic transmission may play an important role in the functional connectivity of distributed brain regions activated during language processing. The effects of dopamine on working memory, a cognitive function involved in syntactic processing, are significant. Administration of the typical antipsychotic medication haloperidol, which blocks dopamine D2 receptors, was associated with reduced verbal working memory performance in schizophrenia patients, compared to their own baseline performance and to the verbal working memory performance of patients receiving the atypical antipsychotic agent risperidone [73]. Working memory performance improved for the patient group receiving risperidone. In contrast to haloperidol, risperidone involves significant serotonin (5-HT2a) and weaker D2 receptor antagonism (for a review, see Ref. [74]). In addition, Castner et al. [75] demonstrated that chronic D2 antagonism, as a result of treatment with haloperidol, produced impaired working memory function in non-human primates. Moreover, working memory function improved in the haloperidol-treated monkeys following brief co-administration of a D1 receptor agonist [75]. D1 receptors in PFC are believed to be important for working memory processes, and those investigators reasoned that the memory dysfunction was due to the haloperidol-induced up-regulation of D2 receptors in the striatum and PFC, and the corresponding down-regulation of D1 receptors in PFC.

In line with those findings, different patterns of association between language function and other cognitive capacities have been observed for schizophrenia patients receiving different regimens of antipsychotic medications (typical versus atypical). In one study, sentence comprehension accuracy ('who did what to whom?') for medicated (56% receiving typical antipsychotics) male schizophrenia patients was not correlated with their general intelligence [23] or semantic knowl-

edge (vocabulary) [29]. In contrast, the comprehension accuracy of healthy individuals was strongly associated with a number of cognitive processes, including general intelligence, semantic knowledge, and verbal working memory capacity. A subgroup of schizophrenia patients in that study was tested during both medication maintenance (haloperidol) and drug-free phases [76]. Although patients' language comprehension accuracy and verbal working memory capacity did not differ between the medicated and drug-free phases, the pattern of correlations between their comprehension accuracy and other cognitive functions did vary between pharmacologic conditions. Patients' comprehension accuracy was not associated with verbal working memory or semantic knowledge during the haloperidol maintenance phase; in contrast, their comprehension accuracy was correlated with verbal working memory during the drug-free phase. In contrast, findings from a separate laboratory for medicated (69% receiving atypical antipsychotics) schizophrenia patients showed strong associations between comprehension accuracy, verbal working memory, and verbal intelligence [20]. Taken together, these various findings implicate dopaminergic transmission as an important influence on a cognitive function (working memory) known to be associated with receptive syntax processes, and, furthermore, may also influence the functional connection between language processes and other cognitive capacities in schizophrenia.

Disturbance in functional connectivity of distributed brain regions active during language processing may also characterize individuals with dyslexia. Horwitz and colleagues [77] found that for non-dyslexic individuals, cerebral blood flow in the left angular gyrus was correlated with cerebral blood flow in the extrastriate occipital and temporal lobe regions during single-word reading. This pattern of association was absent in dyslexic individuals.

The nature of the hypothesized disturbance in functional connectivity of language processes in schizophrenia is not presently understood. Obvious possibilities include selective dysfunction in one or more of the critical cognitive sub-systems, or, alternatively, in the connective linkages (interfaces) between systems. A third possibility is that the cause of schizophrenia produces a generalized cognitive deficit that results in reduced performance in all functional domains. In fact, although schizophrenia patients exhibit performance decrements on a wide range of cognitive tasks, their decreased performance differs significantly from that of non-clinical controls on only some, but not all, tasks. The explanation for this pattern is presently the focus of considerable debate; in particular, the role of task difficulty in patients' variable cognitive performance is highly controversial (for a discussion of this issue, see Refs. [78–80]). Nevertheless, patients' performance variability across cognitive tasks, in conjunction with the patterns of correlation described above, is compatible with a failure in the functional connectivity between different cognitive processes.

The formulation of schizophrenia as a functional disconnection syndrome was first advanced by Bleuler [81], and, more recently, elaborated by Friston [82] and McGlashan and Hoffman [83]. The main premise of the disconnection hypothesis is that the core signs and symptoms of schizophrenia can be explained by a failure to establish and maintain distributed synaptic connectivity. While it is necessary to emphasize that evidence for functional disconnectivity does not automatically entail anatomical disconnectivity, the importance of determining the pathophysiological underpinnings of impaired functional connectivity is assumed. Thus, the structures and cellular dynamics responsible for this failure are of interest. Strong candidate mechanisms include oscillations in the gamma frequency range ($\sim$40 Hz), the nitric oxide (NO) hypothesis of synaptic efficacy, and the white matter of axons.

As a first consideration, rhythmic bursts in the gamma frequency range ($\sim$40 Hz) are believed to promote the synchronization of parallel and spatially distributed activation in cortical and sub-cortical (thalamic) regions (coherence theory) [84,85]. This synchronization may serve to 'bind' or integrate spatially distributed representations into single percepts, and to facilitate memory formation and synaptic connectivity. Findings from recent studies of healthy individuals indicate that the manipulations of experimental tasks produced systematic variations in the cortical oscillations within the gamma frequency range, including language [86,87], semantic memory [88], and associative learning [89]. Moreover, reduced power in the gamma frequency range has been reported for schizophrenia patients [90], and a number of writers have speculated that disturbance in this activation pattern may underlie patients' characteristic disruptions in perception and cognition [29,34,40,91,92]. Gamma frequency oscillations occur during a number of states, including slow-wave sleep (for a discussion, see Ref. [93]), and how this pattern of brain activity results in the putative coherence function remains to be determined. One prominent hypothesis [93] is that gamma frequency oscillations produce binding by synchronizing the responding of excitatory pyramidal cells and inhibitory interneurons located over long distances ($>$1 mm) and with a near-zero phase (timing) lag. Findings from in vitro studies implicate an important role of GABA-ergic activation for this process.

Modulation of synaptic transmission by second messengers provides an additional candidate mechanism for abnormal functional connectivity between spatially

distributed brain regions. Arachidonic acid (AA) [94–97], docosahexaenoic acid (DHA) [98,99], and NO [100,101] influence long-term potentiation (LTP), which is a synaptic correlate of learning and memory that involves an activity-dependent increase in the strength of the excitatory postsynaptic potential (EPSP) [102]. Post-synaptic release of NO has been proposed to play an important role in spatial signaling, synaptic efficacy, and transmitter release. According to the NO hypothesis [103,104], complex spatial and temporal interactions occur between synapses belonging to a neuron group or neural network. NO is believed to be instrumental in the emergence of such neuron groups possibly by altering pre- and post-synaptic efficacy across space. A key element in this proposal is the rapid diffusibility of NO across cell membranes, which enables communication in adjacent areas regardless of whether there are direct synaptic connections. Converging lines of evidence suggest that NO does influence synaptic efficacy within a number of brain regions (hippocampus, cerebral cortex, and cerebellum), as indexed by LTP, and learning and memory processes [101].

The white matter of axons provides an additional locus for the failure in functional connectivity between distributed brain regions. Support for this proposal is currently stronger for dyslexia than for schizophrenia. Structural studies of schizophrenia have generally indicated that gray matter reduction is greater than white matter reduction in schizophrenia, although some data indicate maldistribution of patients' white matter neurons [58]. More direct evidence exists for white matter abnormalities in individuals with reading disorder. Klingberg and colleagues [105] used a measure (anisotropy of diffusion) of white matter microstructure obtained with diffusion tensor magnetic resonanace imaging (DTI) to compare the integrity of white matter in individuals with and without a history of reading disorders. Individuals with reading disorder history were characterized by decreased diffusion anisotropy bilaterally in the temporo-parietal region, with the majority of axons showing an anterior–posterior orientation. This finding has implications for the processing of rapid sequential stimuli, due to the role of white matter in nerve conduction speed, as well as for the connectivity among brain regions recruited during orthographic and semantic decoding.

In summary, the pattern of findings for schizophrenia patients and dyslexics suggests that both disorders may include deficient functional connectivity between the distributed brain regions recruited during language processing. Strong candidate mechanisms for this deficit are oscillations in the gamma frequency range ($\sim$40 Hz), modulation of synaptic efficacy by second messengers, and the white matter of axons.

3. Association of phospholipid abnormalities and language dysfunction in schizophrenia: a tentative hypothesis

Our primary assumption is that receptive language disturbance (reading) in schizophrenia may be caused by a fundamental deficit in the temporal (time-based) dynamics of brain function that includes disruptions to patterns of activation and synchronization. We previously proposed that language disturbance in schizophrenia is due to compromises in two basic cognitive functions: processing of rapid, sequential stimuli; and binding or functional connectivity of processes occurring in distributed brain regions [28,29], and emphasized that it is not known if these basic functions are independent or correlated. However, a primary or core deficit in the temporal dynamics of brain function could cause both disturbances by disrupting patterns of activation and synchronization. Candidate mechanisms and neural pathways were discussed that may be the source of the pathophyisology for these deficits. In this section, it is proposed that language dysfunction in schizophrenia is associated with abnormalities in cell membrane phospholipids, and selected cellular mechanisms that may be involved are detailed. It is additionally hypothesized that a primary deficit of functional excitation originating in the cerebellum, in combination with a compensatory decrease of functional inhibition in the PFC, influences receptive language dysfunction in schizophrenia.

Independent lines of evidence indicate that schizophrenia and dyslexia are both characterized by abnormalities in cell membrane phospholipids. Schizophrenia patients exhibit a number of indicants of phospholipid abnormalities [106], including: reduced plasma arachidonic acid (AA) and linoleic acid, a precursor of AA; decreased red blood cell membrane (RBC) polyunsaturated fatty acids (PUFAs) that were not influenced by typical antipsychotic medication; and reduced incorporation of AA into platelets. Reduced PUFAs, primarily due to decreased AA, have also been observed in the caudate in postmortem tissue [107]. Furthermore, levels of DHA were found to be decreased for schizophrenia patients in skin fibroblast cultures [108] and RBC membrane fatty acids [109]. Of interest, utilization of linoleic acid into AA was similar between schizophrenia patients and controls; in contrast, incorporation of eicosapentaenoic acid (EPA) into DHA was reduced for patients [108]. In addition, in vivo ^{31}Phosphorous Magnetic Resonance Spectroscopy (^{31}P MRS) studies have revealed alterations in central (brain) membrane phospholipid and energy metabolism in the dorsal PFC of schizophrenia patients [110–112], with decreased levels of membrane phospholipid precursors (phosphomonoesters) and increased levels of membrane phospholipid breakdown products (phosphodiesters).

Moreover, peripheral (RBC) PUFAs were correlated with central (brain) phospholipid metabolites (^{31}P MRS) measured in the bilateral prefrontal cortices of schizophrenia patients and healthy individuals [113] thereby indicating that peripheral measures may provide a reasonable analogue for central processes. In parallel, in vivo ^{31}P MRS [114] revealed indicants of increased membrane phospholipid turnover in adult dyslexics compared to non-dyslexics. In addition, the number of clinical signs of fatty acid deficiency (dry skin and hair, excessive water intake, frequent urination) was associated with reading level in children [115], and improvement in adult dyslexics' dark adaptation followed the administration of DHA dietary supplementation [116].

To our knowledge, there is presently no direct evidence for the proposal that abnormalities in cell membrane phospholipids may be associated with receptive language dysfunction in schizophrenia. In the following, a simple trajectory is outlined by which abnormal phospholipid function could result in one type of receptive language dysfunction for schizophrenia. As suggested above, the NO hypothesis of synaptic efficacy [104] may provide a cellular mechanism for our hypothesis of a disruption in schizophrenics' functional connectivity of distributed brain regions activated during language processing. First, NO may play an important role in synaptic efficacy [104], as indexed by LTP. Second, a potential role of DHA in NO production has been recently reported [117], whereby DHA potentiated the interleukin-1β induction of NO synthase (NOS) in vascular smooth muscle cells. This newly characterized set of interactions between DHA, IL-1β, and NOS demonstrates the potentially informative nature of the relationship between brain fatty acid metabolites and NOS. As depicted in Fig. 1, DHA deficits in schizophrenia patients may produce altered NOS induction, and, as a result, altered NO metabolites. Thus, sub-optimal NOS function may lead to compromises in synaptic efficacy, as indexed by LTP, which, in turn, may influence the functional connectivity between spatially distributed brain regions that are recruited during language processing. Other candidate second-messenger pathways include glutamatergic activation of *N*-methly-D-aspartate (NMDA) which stimulates phospholipase A_2 (PLA_2) activity and the subsequent release of AA, the latter of which is also known to influence LTP and to be reduced in schizophrenia.

There are additional important considerations related to the foregoing hypothesis. Alterations in synaptic proteins and NOS expression have been reported for schizophrenia patients. An increase in neuronal NOS expression in the Purkinje cells of the cerebellum was observed in the postmortem tissue of schizophrenia patients [118]. In contrast, a decrease in cNOS (calcium-dependent constitutive NOS) expression in the PFC has been found for schizophrenics [119]. A potential

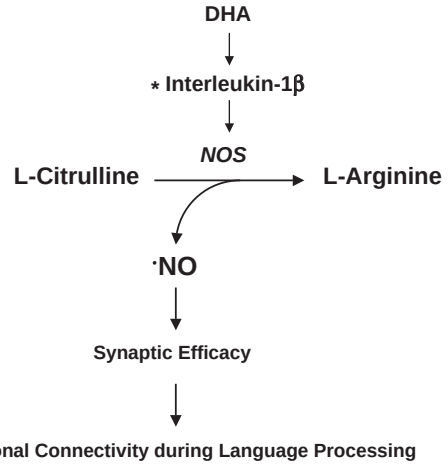

Fig. 1. Hypothesized role of DHA and NO synthase in the functional connectivity of distributed brain regions activated during receptive language processing in schizophrenia patients. *Denotes potentiation. Reduced synaptic efficacy might be expected in regions where DHA and NOS levels are decreased.

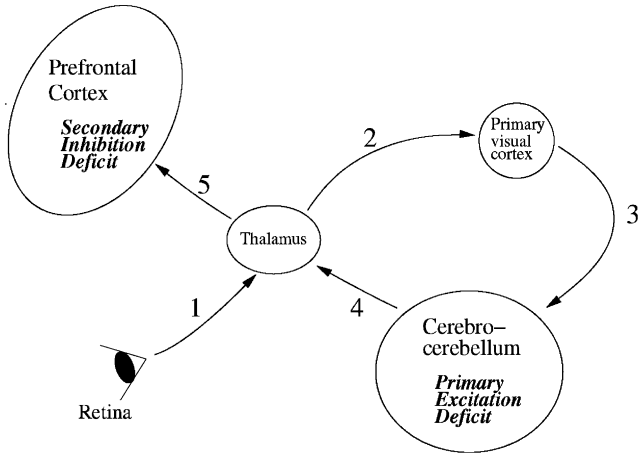

Fig. 2. Hypothesized primary deficit of functional excitation originating in the cerebellum and compensatory decrease of inhibition in the PFC may influence receptive language dysfunction in schizophrenia. This hypothesis is based on evidence involving synaptic protein and second-messenger expression in these regions. Key neural circuitry for visual language dysfunction (reading) in schizophrenia includes activation in the following regions: 1—retina and lateral geniculate nucleus (thalamus), 2—primary visual cortex, 3—cerebrocerebellum (lateral hemispheres and dentate nucleus), 4—thalamus (via dentate nucleus), and 5—PFC. Activation depicted is serial and uni-directional (pathways indexed by arrows 1-5); parallel and modulatory bi-directional (feedback) activation are not shown, but may also be important.

resolution to this apparent discrepancy is that NOS expression could be operating in a compensatory fashion for deficits in excitation by enhancing anatomical connectivity at the synaptic level. Fig. 2 shows a serial, uni-directional neural circuit [59,120,45] and the

hypothesized regional compensatory NOS expression that may be important for visual language processing in schizophrenia: visual language input to the retina activates the lateral geniculate nucleus (thalamus), which is followed by activation of the primary visual cortex, the cerebrocerebellum (lateral hemispheres and dentate neurons), the thalamus via the dentate neurons, and the PFC. (Parallel and modulatory bi-directional (feedback) activation are not shown, but may also be important.) The relevance of a circuit that includes prefrontal–thalamic–cerebellar pathways for language dysfunction in schizophrenia was confirmed by the study of Andreasen and colleagues [67,121] in which decrements in cerebral blood flow were documented for cerebellar and frontal regions.

We therefore propose that the mechanism for the decrement in cerebellar–frontal activation during language processing is a primary deficiency of functional excitation originating in the cerebellum. Additional evidence for this hypothesis is provided by postmortem studies of synaptic proteins in schizophrenia patients. In schizophrenia, postmortem deficiency of an excitatory neuron associated protein has been recorded for the cerebellum. However, postmortem deficiency of an inhibitory neuron associated protein has been documented for the PFC. The synaptic protein phenotypes involved are Complexin I and II. Complexin I is expressed predominantly in inhibitory neurons, whereas Complexin II is expressed primarily in excitatory neurons. In the cerebellum, decreased Complexin II expression was found in the postmortem tissue of schizophrenia patients [122], which may reflect an excitation deficit. In the PFC, decreased Complexin I was observed [123], which may reflect a deficiency of inhibition. The deficiency in excitatory neurons in the cerebellum may cause decreased signal inputs to the PFC. Consequently, the decreased inhibition observed in the PFC may actually be compensatory rather than a primary deficit, thus effecting a compensatory enhancement of the deficient functional excitatory input from the cerebellum. Further compensation for the deficiency of excitatory neurons in the cerebellum may be seen at the dendritic level, with the enhanced nNOS expression observed in this region for schizophrenia patients [118] promoting synaptic density and further boosting functional excitation. The PFC, which does not have a functional excitation deficit, would consequently show the decrease in cNOS expression that, in fact, has been recently reported [119].

In summary, a heuristic is provided that details a hypothetical trajectory involving an interaction of brain fatty acids and second-messenger function, which, in turn, could influence language processing in schizophrenia. It is additionally hypothesized that a deficiency of functional excitation originating in the cerebellum affects receptive language dysfunction in schizophrenia.

4. Summary and conclusions

A relationship between schizophrenia and dyslexia was previously hypothesized that is based on a common abnormality in cell membrane phospholipids [2]. In the present paper, evidence was reviewed indicating that parallels do exist between the patterns of receptive language dysfunction that are characteristic of these two disorders. The causes of language disturbance in schizophrenia were earlier hypothesized to involve compromises in two basic cognitive functions: processing of rapid, sequential stimuli; and binding or functional connectivity of processes occurring in distributed brain regions [28,29]. Discussion in this paper has focused on strong candidate mechanisms and neural pathways that may account for these two cognitive deficits in schizophrenia. Specifically, abnormalities in the magnocellular pathway of the lateral geniculate nucleus in the thalamus and the pathways of the cerebellum may produce deficits in the processing of rapid, sequential stimuli for schizophrenia patients. Abnormalities in the cortical and sub-cortical oscillations within the gamma frequency range, second-messenger function influencing synaptic transmission, and the white matter of axons may create deficits in the binding or functional connectivity between spatially distributed brain regions. It was hypothesized that abnormalities in cell membrane phospholipids may underlie both types of cognitive deficit in schizophrenia. As an initial heuristic, a simple trajectory was provided that includes an interaction of brain fatty acids and second-messenger function that may influence synaptic efficacy, which, in turn, would affect the functional connectivity of brain activation recruited during language processing. It was additionally predicted that a primary deficit of functional excitation originating in the cerebellum, in combination with a compensatory deficit in inhibition in the PFC, may explain some of the receptive language dysfunction of schizophrenia. To our knowledge, there is no direct evidence for the relationships hypothesized to hold between the selected cellular mechanisms, neural pathways, and language dysfunction in schizophrenia. Our goal, therefore, was to describe hypotheses that are necessarily speculative, and to provide indirect links between empirical findings and possible mechanisms for the purpose of suggesting future research directions.

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