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A Social Deafferentation Hypothesis for Induction of Active Schizophrenia

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The "social brain" of humans reflects widespread neural resources dedicated to understanding the conversational language, emotionality, states of mind, and intentions of other persons. A social deafferentation (SDA) hypothesis for induction of active schizophrenia is proposed. Analogous to hallucinations produced by sensory deafferentation, such as phantom limb, the SDA hypothesis assumes that high levels of social withdrawal/isolation in vulnerable individuals prompt social cognition programs to produce spurious social meaning in the form of complex, emotionally compelling hallucinations and delusions representing other persons or agents. Arguments against the SDA hypothesis are discussed, and predictions deriving from the hypothesis are offered.

Key words: social cognition/auditory hallucinations/delusions/social withdrawal

There is an expanding body of research characterizing the "social brain" of humans—those neural resources dedicated to understanding conversational language, emotionality, intentions, actions, and states of mind of other persons based on on-going experience.[1–5] What happens to the "social brain" when opportunities for such experience are drastically curtailed? This question is raised by the fact that social withdrawal is a well-known symptom of schizophrenia. There is evidence that this negative symptom is a consequence of active illness due to amotivation, worsening cognitive impairment, and/or internal preoccupation with psychotic experience.[6–8] It is possible, however, that causality also operates in the opposite direction, namely that social withdrawal is itself an important factor in triggering the initial active phase of schizophrenia. In this article, I will discuss a variant of this view termed the "social deafferentation" (SDA) hypothesis. This hypothesis stems from 3 observations.

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Observation 1: Multiple Studies Suggest that Social Isolation Often Precedes and May Be a Risk Factor for Active Schizophrenia

Kwapil[9] identified college undergraduates with high scores on a Social Anhedonia Scale and compared them with control students. A dramatically increased risk for schizophrenia-spectrum disorders was detected relative to the control group at 10-year follow-up (24% for the high Social Anhedonia group vs 1% for the control group) not accounted for by psychotic-like experiences or rates of substance-use disorders at the initial assessment.

Epidemiologically, an early study by Farnis and Dunham found that living conditions fostering social isolation in Chicago were associated with an increased incidence of schizophrenia, which prompted the authors to hypothesize that "extreme seclusiveness" was a causal factor.[10] This finding was reaffirmed recently using neighborhood-specific identification of new cases of schizophrenia in Maastricht, Holland; factors likely to increase social isolation were associated with increased illness risk.[11] A recent meta-analysis has confirmed that immigration produces a striking increase in risk of schizophrenia.[12] A study of geographic patterns demonstrated that risk was especially high when the migrant group comprised a relatively smaller minority relative to the general population.[13] Being part of a smaller minority group is likely to increase social isolation. These data therefore suggest that social isolation may be a factor mediating risk of schizophrenia among immigrant populations (see also Broome et al.[14]).

Retrospective studies also highlight the potential impact of social isolation as a risk factor leading to schizophrenia. A retrospective study was conducted among a military population who became psychiatrically ill.[15] Among prodromal factors, by far the most robust discriminator of schizophreniform disorder compared with nonpsychotic disorders was social isolation, with 83% in the former group reporting this symptom compared with 3% in the latter. A second retrospective study over a more extended time interval prior to first onset of schizophreniform psychosis found that initial social isolation was first expressed as long as 2–4 years prior to first emergence of psychosis in 57% of cases surveyed.[16] In our own research involving patients with schizophrenia and auditory/verbal hallucinations, we have found that a large

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majority of these individuals have a clear-cut memory of their first experience of "voices." When queried regarding circumstances in the time period immediately prior to these experiences, we were struck by a surprising number of reports of reduced interpersonal interactions. Typical examples include "voices" emerging after moving to a new neighborhood with loss of friends, isolating in an apartment to write a dissertation, driving alone cross-country, or traveling alone to a non-English speaking country. Among the cases surveyed who could recall onset of auditory/verbal hallucinations, increasing social isolation prior to hallucination onset was reported at a rate of 73%.[17] This high rate caused us to reconsider the nature of brain events inducing emergence of these psychotic experiences.

Observation 2: Sensory Deafferentation Produces Large-Scale Brain Reorganization and Complex Hallucinations

Examples of deafferentation syndromes produced by lesions of sensory systems include phantom limb following loss of an extremity, complex visual hallucinations arising from vision loss seen in Charles Bonnett Syndrome and macular degeneration,[18,19] and phantom sensations following spinal cord injury.[20] Deafferentation following sensory loss is known to produce large-scale cortical reorganization.[21–23] Such neuroplastic changes can arise quickly. For instance, depriving normal individuals of sight via blindfolding for as little as 1 hour lowers the threshold for visual phosphenes induced by focal transcranial magnetic stimulation of the occipital cortex indicating sensory hyperexcitability.[24] If this experimental intervention is sustained for a day or more, complex visual hallucinations of faces and shapes in normal persons consistently result.[25]

Observation 3: Hallucinations and Delusions in Schizophrenia Generally Produce Emotionally Compelling, Aberrant Social Meaning

Consider first auditory/verbal hallucinations in schizophrenia, by far the most common type of hallucination reported by this patient group. These hallucinations appear not to reflect random spoken speech but, instead, have consistency in terms of acoustic characteristics ("sounding" like one or more particular nonself speakers). These acoustic characteristics reflect the speaking voices of persons previously known to the patient in about 40% of cases, or if unknown, the "voices" nonetheless come to be experienced as very familiar and recognizable.[26] Verbal content is also distinctive, expressing recurrent themes or messages[17,27] that tend to express highly personal and emotionally charged meaning, often prompting the patient to engage in conversational interaction.[26,28] As such, patients generally report an intimate and intensely personal "relationship" with their "voices" even though content is often highly vulgar, denigrating, or commanding.

Most delusions reported by persons with schizophrenia appear to assign intentions of other persons or agents to environmental stimuli, signs, and signals, which then crystallize into deviant, emotionally charged schema. This outcome involves processing ambiguous input data as interpersonally relevant and referable to the self. For persons with paranoia, attention is paid selectively to information that can be construed as threatening.[29,30] Consider, for instance, ideas of reference. Eye gaze contact is a well-known and critical pathway for communication of social information and emotion.[31,32] For patients with ideas of reference, misattributions of eye gaze contact often lead to or reinforce expectations that others harbor nefarious or otherwise questionable intentions. Indeed, gaze direction discrimination biases of this sort have been demonstrated empirically in patients with schizophrenia.[33] In this study, there was no greater error rate in gaze direction discrimination exhibited by persons with schizophrenia relative to normal controls. A more general error proneness, therefore, did not account for the self-referential eye gaze directional bias detected experimentally, which suggests that the neurocognitive mechanism is specifically geared to producing false attributions of eye contact. More elaborated delusions involving a range of misinterpreted signs and cues lead persons with schizophrenia to "discover" plots and schemes involving real or imagined persons or agents that can be viewed as repopulating a barren interpersonal world.

The SDA Hypothesis: Social Withdrawal During Critical Developmental Periods May Trigger Deafferentation-like Induction of Spurious Social Meaning

Persons with schizophrenia obviously do not suffer from sensory deprivation/deafferentation per se. Nonetheless social withdrawal arises in most cases prior to manifest illness, which is likely to curtail information flow to neural systems responsible for generating complex social meaning. We know from rodent studies that complex brain changes can be induced by experimentally induced social withdrawal which, when applied during rearing, produce some aspects of schizophrenia such as impaired prepulse inhibition.[34,35] We also know that central lesions can produce deafferentation in brain regions other than purely sensory cortical regions (eg, hippocampus and striatum) that trigger dramatic neuroplastic effects.[36,37] Therefore, it is at least plausible that severe social withdrawal in humans during critical developmental periods induces deafferentation-like reorganization in regions of association cortex underlying social cognition that consequently produce spurious experiences with social meaning. A diversity of causes contributing to social withdrawal in the preillness phase is likely (eg, impairments in social cognition and other neuropsychological

deficits, personality factors, depression, anxiety, personal loss, or traumatic events). However, this diversity of causes does not rule out the possibility of a final common pathway leading to initial emergence of schizophrenic psychosis, namely a reorganization of the "social brain" occurring in response to the relative absence of information inflow. To consider the ideas of reference example discussed above, neuroplastic shifts driven by social isolation could cause determination of gaze direction of others to be biased toward detecting eye contact when none occurs in order to generate new (spurious) social meaning. Along similar lines, even though hallucinations and delusions tend to be experienced negatively, they correspond to emotionally charged meaning seeming to derive from other persons that could provide a functional replacement for impoverished social experience.

The SDA hypothesis accounts for the findings of a recent clinical trial testing the rate of conversion to psychosis among patients with prodromal symptoms randomized to placebo or to a second-generation antipsychotic drug.[38] The study included an assessment of the subject's tendency to "hear" distinct words and phrases in response to an experimental sound stimulus consisting of multispeaker babble. The density of phonetic information was so high that only a very few number of words were reliably detected by subjects. The tendency of subjects to "hear" spurious "message-like" phrases in response to this stimulus was shown to be a robust predictor of future risk of conversion to active schizophrenia that was not accounted for by concurrent symptoms or neuropsychological impairment.[39] These findings suggest that the threshold for detecting verbal meaning exhibited by speech perception neural systems was reduced in persons destined to develop schizophrenia, analogous, perhaps, to the lowered threshold of the visual cortex in producing phosphenes elicited by focal transcranial magnetic stimulation when subjects were vision deprived.[24] My hypothesis is that during the preillness state, the capacity of language detection systems to detect complex verbal meaning is ramped up in response to deprivation of ordinary conversational interaction. Individuals in the clinical trial consequently experienced spurious verbal messages repeatedly emanating from ambiguous stimuli in their environment that ultimately may have promoted conversion to active psychosis.

There are least 4 arguments against the SDA hypothesis.

First, not all individuals who suffer from significant social withdrawal become psychotic. Counterexamples include persons with longstanding schizoid personality disorder but no overt psychosis and prisoners who are kept in solitary confinement where rates of new onset of psychosis appear to be relatively small.[40] The SDA hypothesis predicts, however, that the "dose" of social withdrawal that is potentially psychotogenic is determined relative to the person's own prior baseline of social involvement. Moreover, it is plausible that one or more intrinsic vulnerability factors come into play in determining the robustness of neuroplastic response to deafferentation in general and social isolation in particular. Finally, intrinsic factors determining robustness of neuroplastic response to social isolation are predicted to be psychotogenic only during the so-called vulnerable period for schizophrenia (late adolescence and young adulthood). That neuroplastic reactivity to social withdrawal might be especially robust during this time period is suggested by the fact that social identity - the "reference point" for all social meaning - is consolidated independent of family of origin during later adolescence and young adulthood. Thus, the absence of psychosis in schizoid personality disordered individuals and prisoners in solitary confinement may reflect the absence of vulnerability factors reflecting neuroplastic response to deafferentation and/or the fact that the period of social withdrawal did not emerge during the vulnerability period for schizophrenia risk.

Second, not all individuals who develop schizophrenic psychosis expressing social meaning demonstrate preillness social withdrawal. These cases appear to be in the minority, however, and arise perhaps from other factors such as illicit drugs like cannabis.[41]

Third, not all hallucinations and delusions associated with schizophrenia carry social valence. Examples include somatic delusions and hallucinations (see McGilchrist and Cutting[42] for a comprehensive review of these experiences), which are likely due to some other mechanism. However, the predominant psychotic phenomenology arising in schizophrenia does appear to express emotionally charged "pseudosocial" meaning that in theory could arise from SDA.

Fourth, some phenomenological and longitudinal course findings suggest that negative symptoms such as social isolation are worsened by positive symptoms.[43,44] It does seem likely that positive symptoms arising from engagement of the "social brain"—as well as nonspecific disturbances in reality testing and a process of turning inward—would worsen social isolation. However, this view is not inconsistent with the SDA hypothesis. If social withdrawal also worsens positive symptoms per the SDA hypothesis, then a feedforward or autocatalytic process would ensue—with worsening social withdrawal driving positive symptoms and vice-versa in a cascading process—which could account for the relatively rapid decompensations so often exhibited by patients with schizophrenia.

Some Predictions Deriving from the SDA Hypothesis

It would be unrealistic to expect that a single explanatory model will account for all facets and varieties of schizophrenia. Nonetheless, the straightforward logic of the SDA hypothesis—and its potential relevance to

understanding clinical manifestations of most patients—suggests that further testing is indicated. Strategies for testing the hypothesis would reflect the different levels of description captured by this hypothesis.

One approach would be to test psychological treatments that are likely to be efficacious in countering social isolation tendencies (see, for instance, Hogarty et al.[45]) in at-risk prodromal patients. The SDA hypothesis predicts that these interventions would be more efficacious than other psychological treatments in reducing subsequent conversion risk.

A second approach would be to search for neurobiological markers of deafferentation-induced neuroplasticity in components of the "social brain" of persons with schizophrenia. Along these lines, deafferentation has been shown to reduce long-term depression of synaptic excitability in the anterior cingulate cortex.[46] This regulatory process has been linked to the neuregulin-1 (*NRG-1*) gene in one study of the hippocampus.[47] Moreover, reorganization of the olfactory system induced by experimental deafferentation has been shown to be mediated in part by the *NRG-1* gene.[48] These findings are relevant to the study schizophrenia because *NRG-1*, which plays important roles in neuroplasticity (eg, synaptogenesis, neuron-glia communication, and neurotransmission), has emerged as a likely susceptibility gene for this disorder.[49,50] These linkages illustrate the potential merits of the SDA hypothesis in integrating molecular and neural systems findings to account for key clinical manifestations of the schizophrenia.

At very least, this discussion hopefully shows how careful consideration of the nature and content of schizophrenic psychosis in the context of prodromal alterations in psychosocial functioning can lead to a novel neurobiological hypothesis. Testing this hypothesis rigorously is likely to require more sophisticated research methods for assessing the level of and investment in social interaction, characterizing deafferentation-induced neuroplasticity in terms of molecular and physiological features, and comparing these features to those characterizing the neurobiological basis of the positive psychotic manifestations of schizophrenia. There are some who would argue that a theory of schizophrenia attempting to understand the positive symptom phase is not worth the effort—that the primary focus should be on cognitive impairments and negative symptoms. Indeed, social withdrawal hypothesized to produce SDA is likely to reflect neuropsychological and social cognition impairments as well as emergence of other negative symptoms (eg, poverty of speech and avolition) in many cases. However, we must not lose sight of the fact that patients with schizophrenia get treated with drugs carrying significant side effect risks and hospitalized at great expense largely in order to curtail the positive side of the disorder—whose sequelae, if unchecked, are often devastating, if not life threatening. It may be time to again consider positive and negative manifestations of this disorder within a single conceptual framework.

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