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Auditory dysfunction in schizophrenia: integrating clinical and basic features

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Abstract

Schizophrenia is a complex neuropsychiatric disorder that is associated with persistent psychosocial disability in affected individuals. Although studies of schizophrenia have traditionally focused on deficits in higher-order processes such as working memory and executive function, there is an increasing realization that, in this disorder, deficits can be found throughout the cortex and are manifest even at the level of early sensory processing. These deficits are highly amenable to translational investigation and represent potential novel targets for clinical intervention. Deficits, moreover, have been linked to specific structural abnormalities in post-mortem auditory cortex tissue from individuals with schizophrenia, providing unique insights into underlying pathophysiological mechanisms.

Schizophrenia is a severe psychiatric disorder that affects ~1% of the population worldwide[1]. It is diagnosed primarily based on common clinical manifestations, such as agitation, paranoia, delusions and hallucinations (the 'positive' symptoms), and/or apathy, social withdrawal and anhedonia (the 'negative' symptoms). Nevertheless, the impaired psychosocial outcome in schizophrenia is driven primarily by deficits in neurocognitive functions that are manifest across a wide range of cognitive domains. In general, patients with this disorder show a deficit of 1–2 standard deviations in cognitive function, corresponding to a mean reduction in performance IQ to 70–85 (versus the normative value of 100)[2]. The onset of schizophrenia is typically in late adolescence or early adulthood in males (age 17–21 years) and somewhat later in females, and the disorder is associated with

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lifelong disability thereafter[1]. At present, there are no approved treatments that specifically target the neurocognitive impairments in schizophrenia. A key goal of current schizophrenia research, therefore, has been to determine the neural mechanisms underlying these deficits to guide future interventional approaches.

Although neurocognitive studies of schizophrenia have traditionally focused on higher-order functions such as working memory and executive processing, basic sensory functions — including auditory-level function — are also impaired in this disorder and may be particularly amenable to translational, cross-species research. In addition, these deficits contribute substantially to symptoms and overall impairments in psychosocial function. In this Review, we first discuss the evidence for auditory sensory dysfunction in schizophrenia and its underlying mechanisms, particularly the contribution of NMDA receptor (NMDAR) dysfunction and related impairments in glutamatergic and GABAergic function. Neurophysiological approaches, including event-related potential (ERP) and event-related spectral perturbation (ERSP) techniques, have proved particularly effective both for characterizing the clinical deficits in schizophrenia[2,3] and for linking them to underlying pathogenic mechanisms[4], and we thus describe them in detail. We then discuss the mechanisms by which auditory cortical dysfunction leads to the characteristic behavioural manifestations of schizophrenia, especially the impairments in social interaction and communication skills that are tied directly to poor psychosocial function in schizophrenia. Subsequently, we review the structural evidence for auditory cortical involvement in schizophrenia, especially from post-mortem investigations[5], and highlight both the convergences and divergences between the functional and structural findings. We also consider how auditory deficits might relate to existing neurochemical theories of schizophrenia[6,7] (BOX 1).

Behaviour and neurophysiology

In humans, the peripheral auditory system includes the outer ear, middle ear and inner ear, which includes the cochlea. The central auditory system begins with the auditory nerve. Auditory information then ascends via the cochlear nucleus, superior olivary complex and inferior colliculus to the medial geniculate nucleus of the thalamus and then to the auditory cortex (FIG. 1a). The primary auditory cortex (Brodmann's area 41 (BA41)) is located in the posterior third of Heschl's gyrus. By contrast, the secondary auditory cortex (BA42), which includes the lateral belt and parabelt regions, is located in portions of Heschl's gyrus and extends into the planum temporale, encompassing much of the superior bank of the posterior superior temporal gyrus (STG)[8] (FIG. 1b–e). Additional multisensory regions (such as the posterior auditory association cortex — area Tpt) extend to the lateral convexity of the STG, corresponding to BA22, and receive additional crossmodal input. Auditory regions of the cortex have undergone extensive phylogenetic elaboration during primate evolution and also show ontological development, with continued maturation into even the second and third decades of life, and thus are sensitive to potential insults during the risk period for the development of schizophrenia, which probably begins in the early teenage years[1,9].

Peripheral and brainstem auditory function

'Hearing ability' is typically assessed by asking subjects to detect the presence or absence of an isolated auditory stimulus. In general, individuals with schizophrenia have intact performance on routine hearing tests or auditory brain-stem responses, indicating that peripheral and brainstem auditory processing is preserved in such individuals, at least for isolated stimuli[10]. Notably, however, performance on tests of this type is preserved even following complete ablation[11] or inactivation[12] of the auditory cortex in animals or extensive auditory lesions in humans[13,14]; therefore, such tests are relatively uninformative about the existence of potential cortical-level dysfunction. Within the brainstem, NMDARs are involved primarily in complex processes involving plasticity and integration[15]. Such processes have been studied in schizophrenia to only a limited degree but may also be impaired[16], suggesting that dysfunction occurs even at the brainstem level.

Behavioural measures

Although the primary auditory cortex is not critical for the detection of isolated auditory stimuli, it is critical for performing a fine-grained comparison between successive auditory stimuli. Indeed, in animals with bilateral ablations[11,17] or inactivation[12] of the auditory cortex, or in humans with bilateral auditory cortical infarcts[14], the damage leads to a dramatic increase in the threshold for detecting physical differences — such as differences in pitch, duration or location — between successive auditory stimuli. These impairments are observed even in the absence of distracting information (FIG. 2a,b). By contrast, damage to other cortical regions such as the prefrontal cortex does not impair simple tone matching ability, although it does impair the ability to ignore distracting information[17–19] (FIG. 2b).

Individuals with schizophrenia show this 'auditory cortical' pattern of impairments: that is, notable elevations in tone matching thresholds even in the absence of distracting information[20–22], with no further increase in susceptibility to distraction when distracting information is included[23,24] (FIG. 2c). The ability to match tones following a brief delay depends on the formation of an 'echoic' memory trace, which typically decays over a period of 10–30 seconds in both individuals with schizophrenia and control subjects (FIG. 2d). Moreover, when subjects are tested at their individualized tone matching thresholds (FIG. 2e), the decay in performance over time is similar between the two groups, suggesting that the patients with schizophrenia have deficits primarily in the encoding, rather than the retention, of sensory information[24].

Neurophysiological measures

Neurophysiological measures, including those obtained from ERP and ERSP approaches, provide additional evidence for auditory cortical dysfunction in schizophrenia. In ERP analyses (also known as 'time domain' analyses), electroencephalographic (EEG) responses from multiple sensory stimulus repetitions are averaged before analysis in order to separate stimulus-related activity from background EEG responses. This approach is still in widespread use because of its computational convenience. Nevertheless, it discards the significant information that is inherent in the trial-by-trial variability and thus is increasingly being replaced by ERSP approaches. The ERSP approach (also known as the 'time frequency' approach) explicitly embraces the trial-by-trial variability to analyse data at the

ensemble level[4]. In the ERSP approach, EEG responses to individual auditory stimuli are analysed as a function of oscillatory power before averaging, permitting more fine-grained assessment of response patterns. Prominent additional measures obtained in ERSP analyses include single-trial ('induced') power along with the phase locking between successive responses that is measured as inter-trial coherence (ITC)[2,25].

Mismatch negativity

The best established measure for the study of auditory sensory dysfunction in schizophrenia is the auditory mismatch negativity (MMN). The MMN is a widely studied ERP component that reflects pre-attentive processing of the relationship between successive auditory stimuli at the level of the auditory cortex[26–34]. It is elicited most commonly in the context of an auditory oddball paradigm, in which a sequence of repetitive identical stimuli ('standards') is interrupted infrequently and unexpectedly by a physically different, deviant ('oddball') stimulus. Deviant stimuli may differ in any of several physical dimensions, such as pitch, duration, intensity or location (FIG. 3a). As opposed to subsequent auditory ERP components (see below), the MMN is elicited even when subjects are not actively paying attention to the sequence of auditory stimuli (for example, while they are reading a book or performing a visual distractor task) or when there is no behavioural task that requires them to detect the auditory deviants. In humans, generators of the MMN have been localized mainly to the auditory cortex, suggesting that the MMN is generated primarily by neuronal ensembles located in this cortical region[26–29]. Because of the topography of the auditory cortex in humans (FIG. 1c), the voltage distribution associated with the MMN is observed primarily over the frontocentral scalp (FIG. 3b).

Deficits in MMN generation in schizophrenia were first reported in the early 1990s, and these findings have been extensively replicated (FIG. 3b) (reviewed in REF. 10). As with tone matching deficits, the degree of deficit in MMN generation is as large as it is in other well-validated neurocognitive tests, such as tests of executive processing or working memory[30,31]. Deficits in MMN generation in schizophrenia have been reported for multiple types of deviants, including pitch, duration or intensity[32], with little difference in the degree of deficit to different deviance types[32–34].

Furthermore, in individuals showing potential early (prodromal) symptoms of schizophrenia and therefore deemed to be at high risk of developing this disorder, deficits in MMN generation[35,36] and auditory sensory measures[37] precede illness onset and predict which individuals will progress to psychosis. Once present, deficits in MMN persist despite treatment with antipsychotic medications, highlighting the utility of neurophysiological markers for both clinical and translational research approaches.

Other auditory ERP components

Besides the MMN, several other auditory components are localized to the auditory cortex and may be used to probe early auditory function in schizophrenia. For example, auditory P1, a positive potential that occurs with an approximate latency of 50 milliseconds, and N1, a negative potential that occurs with an approximate latency of 100 milliseconds, are elicited by all repetitively presented stimuli, including both standards and deviants in the oddball

sequence. Like MMN, both P1 and N1 are primarily generated by auditory cortical neurons, although neurons in other cortical and subcortical regions may also contribute[38]. In the acute phases of schizophrenia (that is, when individuals are experiencing active hallucinations or other psychotic symptoms), prominent deficits are observed in the gating of auditory P1 and N1 responses to successively presented stimuli, reflecting the impaired ability of patients to filter out irrelevant information[3]. These deficits are thought to reflect dysfunction within brainstem and thalamic networks and have been tied extensively to disturbances in cholinergic function[3]. As opposed to deficits in the MMN, gating impairments largely resolve following treatment with antipsychotics, and tend to be relatively modest once active psychotic symptoms have resolved[31]. By contrast, amplitude reductions in the initial P1 and N1 responses, like those in the MMN, are not only present during the acute phase of the illness but also tend to persist even during antipsychotic treatment, and thus represent components of the illness that are not addressed by existing medications[31,39].

ERSPs

In contrast to ERPs, which primarily reflect brain function at the regional level, ERSPs provide information at the circuit and molecular levels[4]. The majority of ERSP studies in schizophrenia have focused on gamma-frequency (that is, 30–80 Hz) activity using the auditory steady-state response (ASSR) paradigm, in which an auditory stimulus (for example, a click) is repetitively presented at gamma frequencies and cortical responses are measured. Gamma activity, in general, is thought to reflect the interplay between cortical pyramidal neurons and parvalbumin (PV)-expressing interneurons. Consistent reductions are observed in ASSR power and ITC in schizophrenia[40,41], suggesting that impairments exist in synchrony within auditory pyramidal–PV neuron circuits[42]. Consistent with MMN findings, modelling studies suggest that the reductions in ASSR power may reflect reduced NMDAR conductances within superficial pyramidal neurons and fast-spiking interneurons[43]. In rodent models, the NMDAR antagonist ketamine has also been shown to alter the power dependence of ASSR on stimulation frequency[44], leading to a reduction in the amplitude of the ASSR[45].

More recent ERSP studies of auditory dysfunction in schizophrenia have focused on responses within lower-frequency ranges, particularly theta (4–7 Hz) (FIG. 3c). In ERSP analyses, auditory MMN and N1 have been shown to have primary power within the theta frequency band[4,46,47]. As opposed to gamma rhythms, theta rhythms have been tied most closely to the function of somatostatin (SST)-expressing[48] and multipolar bursting-type[49] GABA interneurons. Patients with schizophrenia show increased levels of ongoing theta power and reduced stimulus-induced phase-resetting of theta oscillations in both the MMN and auditory N1 paradigms[47]. This dyad of findings suggests that dysfunction of pyramidal neuron–SST neuron interactions occurs in this disorder in addition to impairments in pyramidal neuron–PV interneuron interactions.

Translational studies

Because auditory ERP and ERSP components such as MMN and N1, and ASSR, respectively, can be elicited even under conditions in which attention to stimuli is not required, these measures are well suited for cross-species investigation. Cellular generators

for auditory ERP or ERSP responses can be localized not only regionally but also by cortical layer[2] (FIG. 3d). The earliest inputs to the cortex are conveyed by thalamocortical afferents that preferentially target the granular (layer 4) and deep supragranular (layer 3) layers. Subsequent activity is observed in supragranular (layer 2/3) and infragranular (layer 6) layers. These same layers can then be identified and analysed in postmortem tissue from patients with schizophrenia (see below). Using intracortical recording approaches, the cellular generators that give rise to the surface P1, ASSR and MMN components have been localized primarily to superficial layers of the cortex, in which they probably reflect current flow within the dendritic tree of superficial pyramidal neurons. By contrast, the cellular generators of the N1 potential localize primarily to deeper cortical layers but may be driven by input from more superficial layers[4] (FIG. 3d).

Neurochemical studies

The availability of model systems also permits the evaluation of potential aetiological mechanisms (BOX 1). The ability of NMDAR antagonists such as ketamine to induce schizophrenia-like deficits in auditory ERP generation was first demonstrated in studies using direct intracranial infusion of NMDAR antagonists into the monkey auditory cortex[29] (FIG. 3e). By contrast, infusion of the type A GABA ($GABA_A$) receptor antagonist bicuculline into the same regions led to a large increase in the local response within both supragranular and infragranular layers (FIG. 3f). The bicuculline-induced increase in response amplitude was, in turn, blocked by NMDAR antagonists, suggesting that local NMDAR-mediated current flow is under marked tonic inhibitory control by local GABAergic interneurons[3].

Since the initial intracranial infusion study, the effects of NMDAR antagonists on MMN generation have been replicated in multiple human[50–55], monkey[56] and rodent[57,58] studies (FIG. 3e) (but see REFS [59,60]). These studies primarily utilized the NMDAR antagonist ketamine, which is suitable for human intravenous administration. In humans, the degree of psychosis that is induced by ketamine negatively correlates with baseline MMN amplitude, suggesting that even some healthy people may have relatively low levels of NMDAR ‘reserve’, which can be indexed by measures such as MMN and might predispose them to developing psychosis when challenged with an NMDAR antagonist[61]. In contrast to ketamine, psychotomimetic agents such as 5-hydroxytryptamine (serotonin) receptor 2A (5-HT_{2A}) agonists (for example, psilocybin[53,62] and dimethyltryptamine[51]), or $GABA_A$ receptor modulators (for example, benzodiazepines)[63] do not inhibit MMN generation[51,62]. Treatment with the NMDAR modulator D-serine ameliorates MMN deficits in schizophrenia[3], supporting the potential use of MMN in translational, treatment-development research[2,7].

Finally, NMDAR antagonists also induce schizophrenia-like changes in other auditory ERP components such as the auditory N1 response[4,64] (FIG. 3f). Following phencyclidine administration in monkeys, deficits are also observed in the generation of the initial P1 potential, probably reflecting effects within both subcortical and cortical auditory structures[3].

Behavioural consequences

In addition to providing strong insights into pathophysiological mechanisms underlying schizophrenia, deficits in auditory function are important because they directly contribute to symptoms and functional impairments that are associated with this disorder. As with the studies of basic auditory functions, both behavioural and neurophysiological approaches have been used to investigate the underlying neural mechanisms of these symptoms and impairments.

Auditory verbal hallucinations

Auditory verbal hallucinations (AVHs) are highly characteristic symptoms of schizophrenia and typically take the form of voices speaking either to or about an individual[65]. Antipsychotic medications markedly reduce AVHs, suggesting dopaminergic involvement in these phenomena. Nevertheless, the majority of patients with AVHs show some persistence of their hallucinations even while receiving antipsychotic medication[66], indicating that other, non-dopaminergic systems may also contribute. In particular, AVHs have been associated with volume loss[67,68] and functional hyperactivity[69,70] of the auditory cortex, suggesting that local pathology within these regions may contribute as well.

Several mechanistic explanations for AVHs have been proposed. First, impaired thalamocortical input to the auditory cortex by itself may have an important role, as AVHs are observed during sensory deprivation[71]. Second, increased synchrony between productive and receptive speech regions, along with reduced suppression of auditory regions during speaking versus listening, may also play a part[72]. Third, AVHs are also associated with reduced MMN amplitudes[73] and impaired predictive coding in the auditory cortex[74], suggesting the involvement of additional local mechanisms. Finally, AVHs may also reflect a failure to correctly localize thoughts in space[75], leading to the perception that they originate outside, rather than inside, the head. Although dopamine agonists and NMDAR antagonists produce only mild AVHs during acute challenge[76], both lead to apparent hallucinatory-like activity during chronic administration in monkeys (for example, attending to or threatening non-existent objects in space)[77–80], suggesting that adaptive changes induced during a persistent hypo-NMDAR–hyper-dopaminergic state may be crucial for their manifestation.

Although AVHs cannot be attributed solely to dysfunction in the auditory cortex, auditory-based treatments may contribute to their clinical management. Thus, inhibitory brain stimulation methods such as low-frequency transcranial magnetic stimulation (TMS)[81] or cathodal transcranial direct current stimulation[82] applied over the auditory cortex are reported to reduce the frequency and the severity of AVHs. The magnitude of these effects has been variable across studies. Nevertheless, a recent meta-analysis reported a 2.9-fold higher response rate to active than to sham TMS[83], with some studies also showing alterations in underlying physiological disturbances such as functional (fMRI) hyperactivity within the superior temporal sulcus[84,85]. The use of physiological approaches to select appropriate candidates[86] and target interventions[87] may lead to further enhancement of therapeutic efficacy for neuromodulatory, brain stimulation-based approaches such as TMS.

Social and role function

In addition to symptoms, auditory deficits strongly contribute to the overall psychosocial dysfunction in schizophrenia[10]. One key process that is affected by impaired sensory capabilities is the ability to interpret the prosody of verbal communications. In Western languages, tonal transitions do not contribute strongly to the perception of individual speech sounds (phonemes) but do convey non-verbal information such as emotion or attitude. For example, happiness is typically accompanied by an increase in both the base pitch and degree of pitch variation in speech, whereas sadness is conveyed by reductions in base pitch and pitch variability[88,89]. Other types of non-verbal information, such as attitudinal prosody ('sarcasm') are also conveyed by subtle shifts in the pitch[90,91]. In schizophrenia, deficits in tone matching strongly correlate with deficits in prosodic processing, including both emotional[22] and attitudinal[91] prosody. These deficits, in turn, lead to impairments in more global aspects of function, such as social and role function (FIG. 4).

In tonal languages such as Mandarin Chinese, tonal information contributes specifically to word meaning. For example, the phoneme 'ya' said with one type of inflection (ya1) means 'tooth', whereas with another inflection (ya4) means 'duck'. Consistent with other auditory findings, Mandarin-speaking individuals with schizophrenia show notable deficits in the ability both to identify and to discriminate words that are phonemically identical but tonally distinct (for example, ya1 versus ya4). As with deficits in prosodic processing and reading in Western languages, deficits in word discrimination in Mandarin-speaking individuals with schizophrenia markedly correlate both with underlying deficits in tone matching ability and with global measures of psychosocial function such as work status[92].

Fluent reading ability also depends on the ability to perceive and manipulate speech sounds (phonological processing). Consistent with other auditory findings, deficits in phonological processing have recently been demonstrated in schizophrenia and lead to a severe degeneration in mechanical reading ability relative to the premorbid state[93]. As expected, deficits in reading were associated with impairments in both basic auditory function on the one hand and overall psychosocial disability on the other[93].

Neurophysiological assessment

Contributions of early sensory dysfunction to subsequent stages of information processing can also be assessed neurophysiologically. For example, in the auditory oddball paradigm, MMN is followed by a later ERP component termed the P300 (P3). As opposed to MMN, P3 is elicited only when subjects are paying attention to the stream of auditory stimuli and must respond (for example, by pressing a button) to a pre-designated target stimulus. Furthermore, generators for P3 are localized primarily to frontoparietal cortical regions, suggesting that they reflect activation of higher-order, heteromodal cortical regions. In one recent study that evaluated MMN and P3 in parallel, marked deficits were observed in the generation of both components in patients with schizophrenia relative to healthy volunteers. Furthermore, a path analysis demonstrated that the deficit in MMN generation accounted for ~50% of the impairment in subsequent P3 generation, supporting bottom-up contributions to the dysfunction in later stages of auditory information processing[30].

Similarly, a recent fMRI study in patients with schizophrenia showed that the failure to generate MMN led to marked reductions in the activation of structures within the salience network, such as the insula and the anterior cingulate cortex. In addition, MMN deficits led to failures of inactivation of the visual cortex and other structures that are not required for auditory processing[94]. Thus, to the extent that MMN functions to attract voluntary attention to potentially salient environmental events, the failure of this process in schizophrenia serves to disconnect individuals with schizophrenia from the environment.

ERSP analyses can be similarly informative. Many environmental events, such as speech, occur with cadences in the delta frequency range (0.5–4 Hz). In experimental paradigms, repetitive auditory stimuli are also typically presented at delta frequencies (for example, interstimulus intervals of 250 ms–2 s), mimicking the natural situation[47]. During normal function, the brain entrains ongoing delta rhythms to the cadence of the presented stimuli to predict when the next stimulus will occur (FIG. 5a). This process allows the brain to bring maximal processing resources 'online' specifically when the next stimulus is anticipated, as reflected in modulation of ongoing gamma rhythms[25,95]. Individuals with schizophrenia do not show either the increase in entrainment (as reflected in delta ITC) with increasing task difficulty (FIG. 5b) or the task-related modulation in gamma activity[47]. Failures in entrainment are, in turn, strongly associated with the elevated tone matching threshold and impairments in P3 generations that are observed in schizophrenia[47]. Deficits in auditory entrainment persist even when subjects are tested at their individualized thresholds and therefore show similar overall accuracy in the task, suggesting that these deficits contribute to information processing deficits in schizophrenia over and above the processes that give rise to MMN and theta generation deficits.

Although neural mechanisms underlying delta activity generation are still being investigated, delta generators have recently been characterized in isolated rodent cortex and have been shown to reflect an interaction between NMDAR-driven intrinsic bursting cells in deep cortical layers and $GABA_B$ receptor-driven inhibitory feedback loops[96]. If these findings are confirmed, they suggest that failure of delta entrainment may represent an additional mechanism by which NMDAR dysfunction leads to higher-level cortical impairments across cortical regions and that the auditory cortex may represent an ideal model system in which to investigate underlying neuronal mechanisms.

Structural and histological findings

Consistent with the impairments of auditory function and neurophysiology, neuroimaging and post-mortem histology studies have also shown structural changes in auditory regions of individuals with schizophrenia. These findings have provided convergent insight into the neural substrates underlying impaired auditory processing in schizophrenia.

Structural neuroimaging findings

Reduced STG volume is among the most consistently reported MRI alterations in schizophrenia (reviewed in REF. 97). Furthermore, volume reductions in this structure are already present at[98–100] or even before[101] the initial diagnosis of schizophrenia, and thus do not seem to be an artefact of medication or prolonged illness duration. Grey matter volume

reductions in the STG are not found in the closely related condition bipolar disorder with psychosis[98,99], suggesting that pathology of this structure may be specific to schizophrenia. Similarly, STG volume reductions are not induced by alcohol dependence[102,103] and thus are not likely to arise even from extensive alcohol use in patients with schizophrenia.

Consistent with functional findings, structural changes also extend to Heschl's gyrus (FIG. 1e). Although an early report indicated that there were no such changes in this brain region[104], several subsequent studies have demonstrated that individuals at their first episode of psychosis show reduced Heschl's gyrus grey matter volume compared with healthy volunteers and patients with bipolar disorder with psychosis[99,100,105]. This accelerated volume loss is not readily attributable to antipsychotic treatment, as patients with bipolar disorder with psychosis also received such treatment[105]. STG grey matter volume reductions are also accelerated in individuals with early, subthreshold symptoms (clinically high-risk subjects) who later develop psychosis, relative to high-risk subjects whose symptoms nevertheless remit[106]. Similarly, in individuals with schizophrenia, grey matter volume loss is also observed in Heschl's gyrus and the STG after the first presentation of psychosis, relative to both healthy controls and subjects with bipolar disorder with psychosis[100,105,107]. Thus, during a period surrounding the adolescent onset of first psychosis, patients with schizophrenia show progressive grey matter alterations within the auditory cortex.

Post-mortem studies

Consistent with structural MRI findings, post-mortem studies have found reductions in STG grey matter volume in individuals with schizophrenia[108–112]. Early studies primarily utilized morphometric measurements to assess cortical thickness and/or neural volume, whereas more recent approaches have used antibodies directed against cellular proteins to differentiate neuronal subcomponents, projection pathways and cell types in assessments of structural integrity. Targets that are used in the assessment of glutamatergic neurons include spinophilin (also known as neurabin 2), which is localized within dendritic spines[113], and vesicular glutamate transporter 1 (VGluT1) and VGluT2, which are localized within presynaptic glutamatergic terminals of cortical and thalamic origin, respectively[114]. The assessment of GABAergic interneurons has relied on targeting of the GABA-synthesizing enzyme glutamate decarboxylase 65 (GAD65; also known as GAD2), which is expressed by multiple interneuron cell types[115,116]. These approaches, and an initial targeted proteomic study[117], have further contributed to the assessment of expression levels of proteins involved in glutamate and GABA signalling.

Glutamatergic pyramidal neuron structure

In the auditory cortex, the tonotopic organization is linked to local circuit processing in the superficial pyramidal cell layers. Thus, although tone frequency is encoded at all levels of the auditory system, the broad frequency representations at lower levels are refined within the primary auditory cortex via the reciprocal connections of layer 3 pyramidal cells[118,119]. Dendritic spines on pyramidal neurons receive the majority of glutamate synapses within the cortex. Nearly half of dendritic spines on layer 2/3 neurons of the auditory cortex receive

narrowly tuned frequency inputs, and thus can serve to spatially and biochemically segregate frequency tuning within individual dendrites and neurons[120].

Immunocytochemical studies have investigated the integrity of supragranular pyramidal cells within the auditory cortex in schizophrenia. An initial report found a 27% reduction in dendritic spine density in deep layer 3 of the primary auditory cortex in individuals with schizophrenia, as revealed by the detection of spinophilin using immunolabelling[113]. A follow-up study that used a more refined technique in which spines were defined based on the colocalization of spinophilin and filamentous actin (detected by immunolabelling and phalloidin staining, respectively) found a decrease in spine density of a similar magnitude[121]. Importantly, the reductions in spine density did not result from a loss of pyramidal neurons, which were unchanged in number[122], but instead from a reduction in the number of spines per neuron, potentially leading to a reduction in neuronal connectivity. The reductions in spine number could also not be attributed to long-term antipsychotic treatment. Functionally, the reduction in layer 3 dendritic spines would be anticipated to reduce the separation of inputs representing different frequencies, and is thus consistent with a potential contribution to deficits in MMN generation and frequency discrimination in schizophrenia[26,29].

In contrast to the reduction in dendritic spines, there was no evidence for a reduction in the density of VGluT1-immunoreactive presynaptic boutons (arising from cortical glutamatergic neurons) in deep layer 3 of the primary auditory cortex[114]. This mismatch between bouton density and loss of the spines onto which they normally synapse may lead to more boutons making synapses directly onto dendritic shafts — a phenomenon that has been demonstrated to occur at the rat CA3–CA1 synapse after chronic AMPA receptor blockade[123,124], as well as in post-mortem anterior cingulate cortex tissue from patients with schizophrenia[125]. If such a rearrangement was also present in the auditory cortex, it would be likely to interfere with frequency discrimination, as spines both segregate frequency inputs[120] and normalize the magnitude of excitation produced by inputs targeting the dendritic tree at different distances from the soma[126]. Thus, subtle alterations in synaptic targeting may lead to substantial effects on local circuit processing of frequency or other auditory information, as observed in schizophrenia.

Thalamocortical glutamatergic projections

The primary auditory cortex receives its main afferent input from the medial geniculate nucleus (FIG. 1a). Although the medial geniculate nucleus has not been directly studied in post-mortem tissue of individuals with schizophrenia, one study showed that the density of VGluT2-immunoreactive boutons in the thalamocortical recipient layer of the primary auditory cortex (that is, deep layer 3) was unchanged[114]. In general, detection of a sound depends on subcortical processing, whereas processing of the relationship between tones depends on local processing within the auditory cortex (see above). The observations that the thalamocortical input is intact but that there is a reduction in dendritic spine density in the supragranular cortical layers are thus consistent with the findings that individuals with schizophrenia have intact simple auditory detection thresholds but impaired tone matching abilities, and ERP and ERSP abnormalities.

Glutamatergic function

The reductions in dendritic spine density described above strongly support the hypothesis that postsynaptic glutamatergic function is altered in the auditory cortex in schizophrenia. Several other findings provide additional support for this hypothesis. A recent targeted proteomic analysis of 155 synaptic proteins in the primary auditory cortex tissue found that schizophrenia is associated with the altered expression of various glutamatergic signalling proteins[117]. The two most significantly reduced proteins were GluR3 and GluR4, which are calcium-permeable subunits of AMPA receptors. NMDAR protein levels, however, were found to be unchanged. There is also marked reduction in immunoreactivity for the micro-tubule-associated protein 2 (MAP2), which is a regulator of dendritic plasticity that is itself regulated by signalling through glutamate receptors[127], in the auditory cortex of individuals with schizophrenia[121].

The preservation of intracortical and thalamocortical glutamate bouton density does not necessarily mean that these boutons are functionally intact in schizophrenia. For example, the expression of presynaptic proteins such as synaptophysin is reduced throughout the brain in schizophrenia[128,129], including in thalamorecipient layers of the auditory cortex[130]. Although synaptophysin is found in nearly all boutons that release classic neurotransmitters[131], the vast majority of such boutons in layer 3 are glutamatergic.

Furthermore, *in vitro* studies suggest that synaptophysin reductions can impair glutamate signalling. For example, cultured hippocampal neurons from synaptophysin-knockout mice exhibit a pronounced synaptic depression during sustained activity and a slower recovery of recycling vesicle pools after their depletion[132]. The reduced expression of the presynaptic protein synapsin 1, which may also impair glutamate release during repetitive firing[133], has also been reported in the primary auditory cortex of individuals with schizophrenia[117]. By contrast, the expression levels of VGluT1 and VGluT2 within glutamatergic boutons are preserved in this brain region, suggesting that the packing of glutamate into vesicles and quantal response upon vesicle release would be intact.

Reductions in presynaptic proteins may affect post-synaptic pyramidal neuron structural integrity. Because deafferentation of glutamatergic projections is known to lead to decreased spine density[134–137], reductions in synaptophysin within glutamate boutons in layer 3 of the primary auditory cortex might contribute to functional glutamatergic deafferentation, consistent with the observation that reductions in synaptophysin punctum density and spine density are correlated in the auditory cortex of individuals with schizophrenia[113]. Reduced spine density (albeit in the somatosensory cortex) was also observed in a rodent model of schizophrenia that is based on NMDAR hypofunction (the serine racemase-knockout mouse)[138], again supporting a convergence between the findings from pharmacological and physiological models of the disorder.

GABAergic local circuit interneurons

There is evidence for functional but not structural changes in inhibitory neurons in the primary auditory cortex in schizophrenia. Inhibitory neurons in the human cortex (including the auditory cortex; see FIG. 6) are differentiated by their laminar position, connectivity,

firing pattern, expression of calcium-binding proteins and neuropeptides, and usage of GABA-synthesizing enzyme GAD65 versus GAD67 (also known as GAD1)[115]. GAD65 may be particularly important for GABA synthesis in interneurons displaying the high firing rates that are needed to maintain gamma-range oscillations[139], such as PV-expressing basket cells[115,140]. Changes in GAD65 levels in schizophrenia may therefore have a role in the disturbances in generation of auditory gamma oscillations in schizophrenia[2].

It is therefore perhaps not surprising that levels of GAD65 protein are reduced by ~40% within inhibitory boutons in deep layer 3 of the auditory cortex in individuals with schizophrenia[141], although at present it is not known whether this reduction is present in PV-expressing basket cells, as other GABA cell types implicated in schizophrenia also express GAD65 (REF. 116). Determining whether alterations in the GABA cells supporting gamma oscillation generation contribute to the cause of symptoms in schizophrenia, or whether they are homeostatic compensations in response to a reduction in the number of glutamatergic inputs, is complex, and these issues are not currently resolved[42]. However, it is worth noting that, in cell culture and rodent models, NMDAR antagonists induce the release of inflammatory cytokines (for example, interleukin-6) and the downregulation of PV expression[142]. In rodents, conditional knockout of NMDAR from cortical and hippocampal GABA cells in early postnatal development also leads to reductions in GAD67 and PV expression during adulthood along with reduced neuronal synchrony[143], providing a potential additional mechanism for PV reduction in schizophrenia. However, whether this mechanism accounts for the PV interneuron deficits that are observed in post-mortem tissue from patients with schizophrenia remains to be determined[42].

Pathological findings in other cortical regions

Many of the glutamatergic alterations in schizophrenia, described above, are not unique to the primary auditory cortex. Alterations in the morphology of pyramidal neurons, including dendritic spine density reductions, have been reported in additional cortical regions, including the auditory association cortex, temporal association cortex, pre-frontal cortex and hippocampal formation. Reductions in expression of the presynaptic protein synaptophysin have similarly been reported in the same regions, except the auditory association cortex. Although less thoroughly studied, reductions in AMPA receptor subunit protein levels have also been reported in the hippocampus and the prefrontal cortex from patients with schizophrenia. It is not known whether the conservation of these alterations across regions contributes to symptoms by directly affecting the circuit elements that connect regions, or whether they contribute to symptoms by altering the circuits responsible primarily for the local processing within each region, or both (reviewed in REF. 5).

Conclusions

Sensory processing was once considered an “intact simple function” (REF. 144) in schizophrenia. However, more recent studies have demonstrated that even basic auditory processes, such as tone matching, are severely impaired in schizophrenia and also contribute directly to impairments in overall social and cognitive functioning — core symptoms of this disorder. The striking convergence of findings observed in behavioural, neurophysiological,

neuroimaging and post-mortem studies of schizophrenia suggest that the auditory cortex represents a fertile ground for future aetiological investigations involving both human and animal studies. Moreover, to date, these findings strongly support models of schizophrenia that involve dysfunction of glutamatergic and NMDAR circuits throughout cortical regions.

In addition, the findings described in this article indicate that a primary cause of psychosocial dysfunction in schizophrenia is, at present, underappreciated and undertreated. The onset of schizophrenia typically occurs during university age, and patients with schizophrenia rarely return to their former level of academic or role function even after their symptoms have been stabilized. Deficits are frequently attributed to disturbances in complex processes such as attention or working memory, whereas basic functions such as auditory discrimination and reading ability are rarely tested. If detected, such deficits could potentially be targeted with the types of remediation programmes that have been developed for the treatment of specific developmental dyslexias, congential amusia (tone deafness) or other auditory processing disorders. The convergence between the clinical and post-mortem findings suggests that impairments in auditory function in schizophrenia are not downstream consequences of dysfunction elsewhere in brain, but instead reflect functional consequences of local cortical pathology.

Although the present Review focuses entirely on the auditory system, similar deficits are present in other sensory modalities[3,10,145], particularly the magnocellular visual system[146], and are also associated with structural deficits in underlying cortical regions[147] as well as potential impairments in NMDAR function[148]. Measurements of sensory function are not included in standard neurocognitive assessment batteries for schizophrenia, such as the MATRICS consensus cognitive battery[149]. The present findings call for greater focus on sensory dysfunction in both clinical and research settings, and greater use of sensory functional measures in both translational and aetiological research.

Glossary

Event-related potential (ERP)	An alteration in ongoing electroencephalographic activity that is elicited by specific sensory, motor or cognitive events, and is measured as a function of mean amplitude over time (‘time domain’ response)
Event-related spectral perturbation (ERSP)	An alteration in ongoing electroencephalographic activity that is elicited by specific sensory, motor or cognitive events, and is measured as a function of mean alteration in spectral amplitude and inter-trial coherence over time (‘frequency domain’ response)
Tone matching	The ability to compare the physical properties between successively presented stimuli. It is disrupted by auditory cortical lesions in both humans and non-human primates
Mismatch negativity (MMN)	A component of an event-related potential that reflects NMDA receptor-mediated information processing within the auditory

	sensory cortex, permitting its use as a translational biomarker of NMDA receptor dysfunction in schizophrenia research
Gating	The reduction in the amplitude of the response to a second stimulus compared with amplitude to the first stimulus in a paired auditory stimulus
Antipsychotics	Medications typically used in the treatment of schizophrenia that primarily act through dopamine D2- and 5-hydroxytryptamine 2A-type receptors
Ketamine	A well-studied non-competitive NMDA receptor antagonist that induces transient schizophrenia-like symptoms in healthy human volunteers and schizophrenia-like event-related potential abnormalities in non-human primates
Prosody	The ‘musicality’ of speech, which is used to convey non-verbal information such as emotion or attitude

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Box 1

Model psychoses and neurochemical conceptualizations of schizophrenia

The aetiological mechanisms of schizophrenia remain unclear. Currently, there are two major neurochemical models for this disorder: the dopaminergic and glutamatergic models.

The dopamine model is based on the fortuitous observation that the compound chlorpromazine had dramatic and unexpected effects on symptoms of schizophrenia[150]. These effects were later tied to the blockade of D2-type dopamine receptors[151]. In parallel, the ability of psychostimulants, such as amphetamine, to induce schizophrenia-like psychotic symptoms was found to be tied to their stimulatory effects on dopaminergic systems in the brain[152]. Currently, all approved compounds for schizophrenia, including both typical and atypical antipsychotics, induce antipsychotic effects primarily by blocking neurotransmission at dopamine D2 receptors[153,154]. Nevertheless, dopaminergic models are limited both by the inability of current antipsychotic agents to reverse the core negative symptoms and neurocognitive impairments associated with schizophrenia, and by the inability of psychostimulants such as amphetamine to induce such symptoms in healthy human volunteers.

Glutamatergic models are based on the observation that phencyclidine, ketamine and other ‘dissociative anaesthetics’ induce schizophrenia-like symptoms and neurocognitive deficits by blocking neurotransmission at NMDA receptors (NMDARs)[6,7]. Such agents induce both negative and positive symptoms in healthy volunteers[155,156] along with schizophrenia-like neurocognitive and neurophysiological deficits such as impaired generation of mismatch negativity (MMN)[29,50]. Moreover, NMDAR agonists such as glycine, D-serine and *N*-acetylcysteine have shown beneficial effects on symptoms and neurophysiological deficits in small-scale treatment studies of schizophrenia[157], including studies involving individuals at clinical high risk for this disorder[158], although these findings are yet to be confirmed in larger-scale investigations[157,159].

Other neurotransmitter systems may also be involved in schizophrenia. For example, disturbances in GABAergic neurotransmission occur during the course of the disorder[42] and are specifically linked to impaired generation of high-frequency (gamma band) oscillatory activity such as that observed during the auditory steady-state response[42]. However, to date, GABAergic agents have not proved effective in the treatment of schizophrenia[160]. Cannabinoids, such as tetrohydrocannabinol (THC), also induce schizophrenia-like symptoms, in part by inducing a hypoglutamatergic state via CB1 receptors[161]. Agents that target the 5-hydroxytryptamine (serotonin) receptor 2A (5-HT_{2A}) such as psilocybin[62] and dimethyltryptamine (DMT)[51] also induce schizophrenia-like positive symptoms and deficits in prefrontal functioning in healthy human volunteers. Nevertheless, these compounds do not induce negative symptoms resembling those of schizophrenia or inhibit MMN generation[51,62,162], suggesting a potential role of 5-HT_{2A} dysfunction in the positive symptoms but not the negative symptoms or neurophysiological impairments in schizophrenia.

Both genetic and environmental factors may also have key roles in the pathogenesis of schizophrenia. The concordance rate among identical twins for schizophrenia is high (~50%), suggesting that this disorder has a strong genetic component. Nevertheless, this figure suggests that what is inherited is a susceptibility to schizophrenia rather than the disease itself. Associations have been reported between schizophrenia and the genes for both the D2 receptor and NMDAR, as well as between schizophrenia and genes that affect NMDAR function more generally (for example, the gene encoding serine racemase)[163]. Environmental factors including autoantibodies against the NMDAR[1,164] may also contribute to the risk of schizophrenia and may provide additional therapeutic targets.

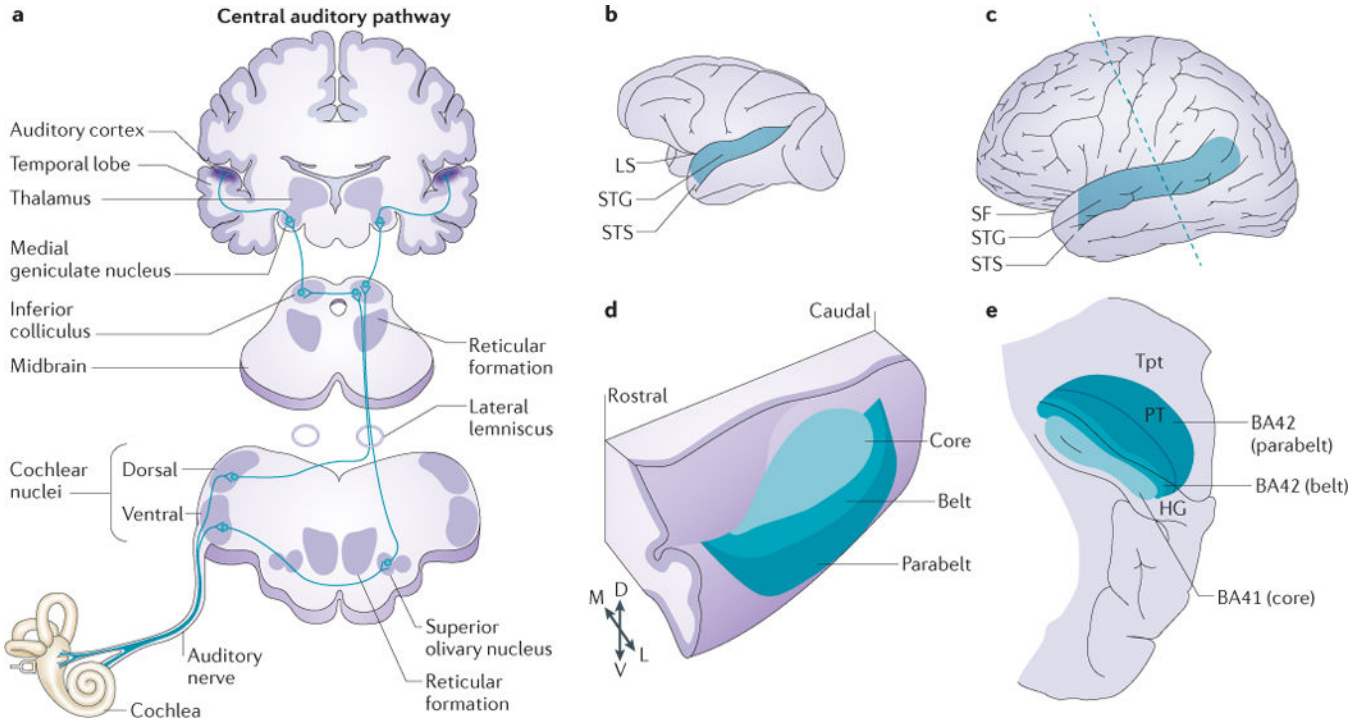

Figure 1. Anatomy of the auditory pathway and the auditory cortex

The ascending auditory pathway in humans begins as the auditory nerve enters the brainstem, where it forms synapses in the dorsal and ventral cochlear nuclei (part **a**). Projections from the dorsal cochlear nucleus cross the midline and travel through the lateral lemniscus to synapse in the inferior colliculus. Neurons of the inferior colliculus project to the medial geniculate nucleus of the thalamus, which provides innervation to the auditory cortex. The auditory cortex location (in grey) in monkeys is shown in part **b** and in humans is shown in part **c**. The superior temporal gyrus (STG) is bordered superiorly by the lateral sulcus (LS) in monkeys and the Sylvian fissure (SF) in humans. Inferiorly, the STG is bordered by the superior temporal sulcus (STS) in both monkeys and humans. The blue dashed line shows the orientation of electrical currents generated within the auditory cortex. Because of this orientation, human auditory event-related potentials show a characteristic topography over the surface of the scalp, with inversion of activity between frontocentral scalp regions and mastoids (for example, see FIG. 3b). Diagrams of the regions that make up macaque (part **d**) and human (part **e**) auditory cortices are shown. The primary auditory cortex, denoted as the auditory core in monkeys, and as Brodmann's area 41 (BA41) in humans, is indicated. In humans, BA41 is located in the posterior medial two-thirds of Heschl's gyrus (HG). In monkeys, the auditory association cortex is subdivided into lateral belt and parabelt cortices, which together comprise BA42 in humans, in a location extending from the lateral portion of the HG onto the planum temporale (PT). The view is from above the STG, after removing the overlying cortex, revealing the superior temporal plane. Tpt, heteromodal temporoparietal region.

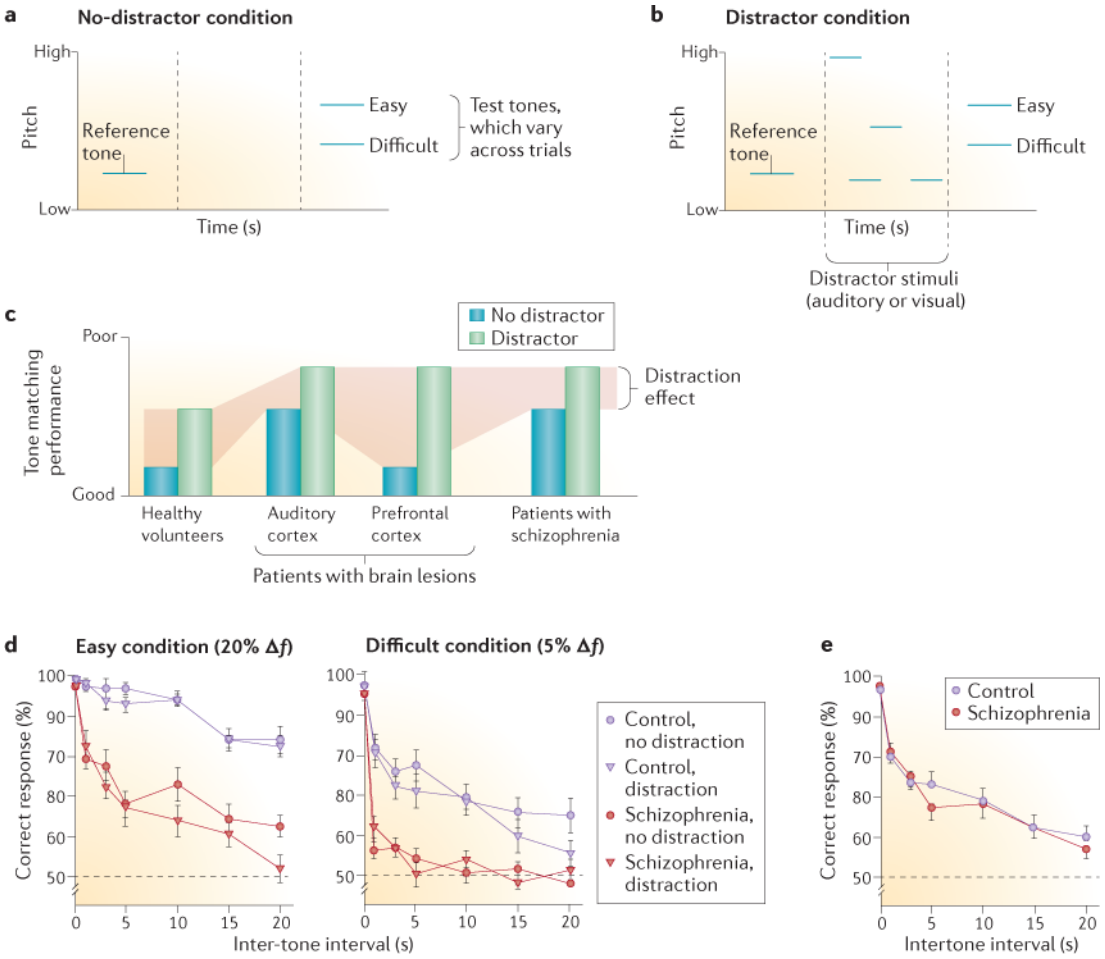

Figure 2. Tone matching deficits in schizophrenia

Although the majority of cognitive studies in schizophrenia use relatively complex paradigms, such as those investigating executive processing or working memory, deficits are observed even in relatively simple auditory paradigms, such as the ability to match tones following a brief delay. In this paradigm, tones are presented sequentially, and subjects must report whether the second tone is the same or different from the first or higher or lower in pitch. The difficulty of the task is defined by altering the pitch difference between the reference and test tones. **a,b** | Stimuli can be presented either in a no-distractor condition in which the interval between tones is silent, or in a distractor condition in which irrelevant auditory stimuli or visual stimuli are presented in the intervening period. **c** | In all individuals, presentation of distractor tones between the reference and test tones leads to an elevation in discrimination thresholds, which are expressed as the difference in tone frequency between stimuli (Δ*f*). Individuals with lesions that affect the auditory cortex show elevated thresholds even in the absence of distractors, but no increased susceptibility to distraction[14]. By contrast, individuals with lesions that affect the prefrontal cortex do not have elevated thresholds in the absence of distraction even at relatively long interstimulus intervals (for example, 5 seconds), but show increased susceptibility to distraction effects[165]. Individuals with schizophrenia show elevated tone matching thresholds even in the absence of distraction, but are no more susceptible to distraction than controls[23], supporting the

concept of auditory cortex-level dysfunction. **d** | In addition to having a normal ability to ignore auditory distractors, patients with schizophrenia show normal retention of auditory tonal information once a correction is made for the increased overall thresholds. In the experiment shown in the figure[24], tones pairs were presented at two difficulty levels (easy (20% Δ*f*) and difficult (5% Δ*f*)) with (triangles) and without (circles) a distraction condition (in which subjects had to count aloud). The subjects were asked whether the first and second tones were the same or different (chance performance (dashed line) was 50%). As expected, patients (open symbols) performed worse than controls (closed symbols) at both difficulty levels. The presence of distraction had equivalent effects in both groups only at the longest interstimulus interval. **e** | Crucially, when the performance of patients performing the easy discrimination task was compared with that of controls performing the hard discrimination, performance decay curves were overlapping over the 20-second interval. These findings indicate that once a correction is made for the deficit in encoding of tone difference, retention of sensory information is unimpaired in schizophrenia, which is also consistent with primary auditory cortical pathology. Error bars in parts **d** and **e** represent s.e.m. Parts **d** and **e** are Copyright © 1997 by the American Psychological Association. Modified with permission. The official citation that should be used in referencing this material is Impaired precision, but normal retention, of auditory sensory (“echoic”) memory information in schizophrenia. Javitt, Daniel C.; Strous, Rael D.; Grochowski, Sandra; Ritter, Walter; Cowan, Nelson *Journal of Abnormal Psychology*, Vol **106**(2), May 1997, 315–324. The use of APA information does not imply endorsement by APA.

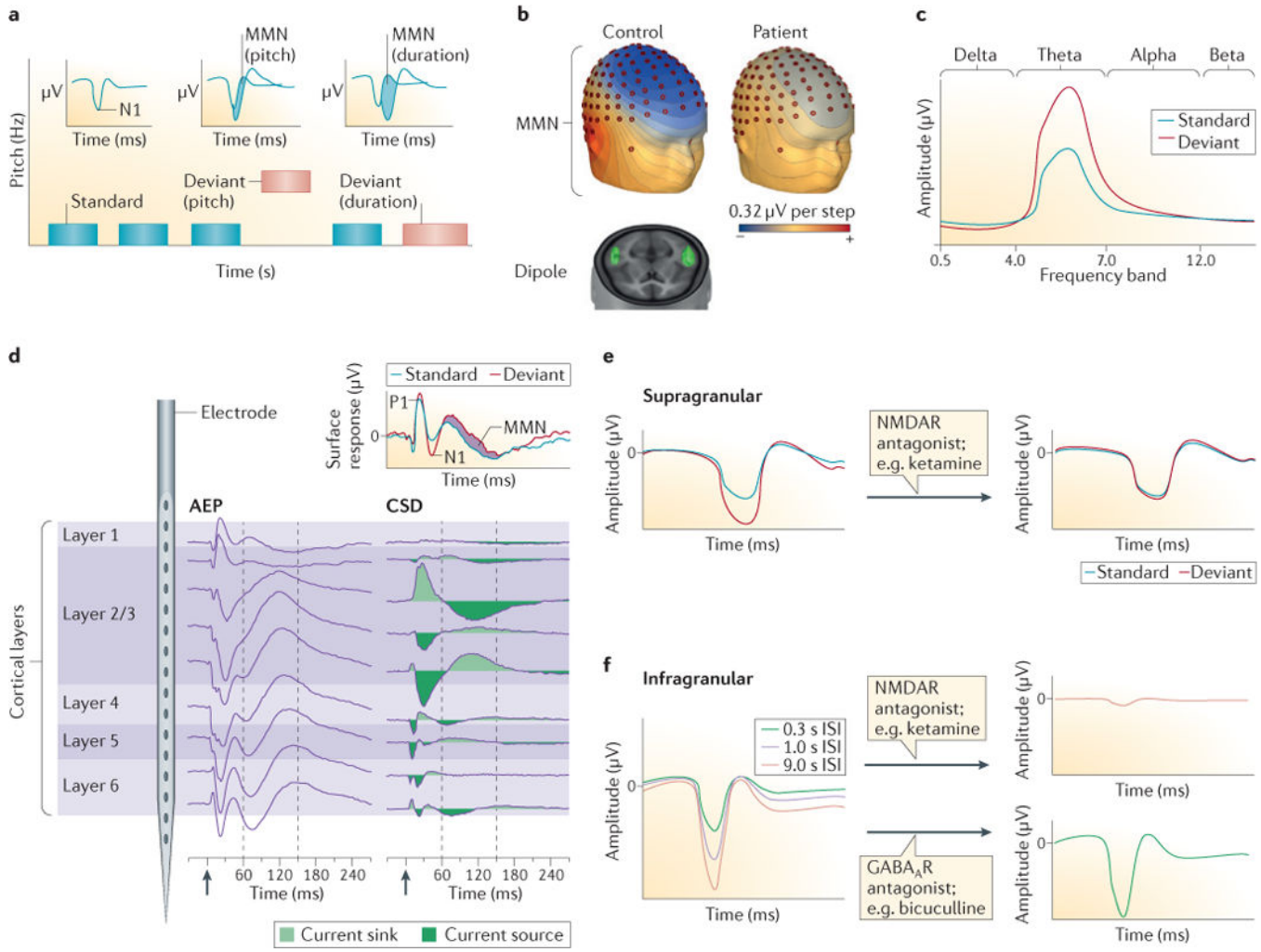

Figure 3. Translational utility of auditory neurophysiological responses

Deficits in tone matching may also be observed using electrophysiological, event-related potential (ERP) or event-related spectral perturbation (ERSP) paradigms. **a** | In the auditory 'oddball' paradigm, a sequence of repetitive standard tones is interrupted infrequently and unexpectedly by a physically deviant oddball stimulus. Oddball stimuli may differ from standards in any of a number of physical dimensions, including pitch, duration, intensity, location or even in abstract features such as stimulus omission. In this paradigm, both standard and deviant stimuli elicit an auditory N1 potential that reflects the response of the auditory cortex to the physical properties of each stimulus in isolation. Deviant stimuli elicit an additional ERP component termed mismatch negativity (MMN) that reflects a comparison between successive stimuli, and is calculated as the difference in response to the deviant versus the standard tone (shaded region in part **a**). MMN for duration deviants is delayed relative to that for pitch deviants, because pitch deviance can be determined at stimulus onset, whereas duration deviance can only be determined at expected stimulus onset. This property further distinguishes MMN from N1, which is unaffected by alterations in stimulus pitch or duration. **b** | The MMN is distributed over the frontocentral scalp, consistent with generators that are located primarily in the supratemporal auditory cortex

(FIG. 1c). The figure shows a voltage topography map of MMN-related electrical activity over the surface of the scalp, with blue representing more negative electrical activity and red more positive activity[32]. Patients with schizophrenia show MMN amplitudes that are reduced by approximately 50% relative to controls (top panels). Dipole mapping analyses (bottom panel) show that the primary generators of the MMN are in the left and right auditory cortex[46]. Deficits in tone matching and MMN generation are significantly interrelated[46], and are consistent with functional and structural impairments at the level of the primary auditory cortex. **c** | ERSP analysis of the MMN response. As opposed to the auditory steady-state response (ASSR) that has primary power within the gamma (30–80 Hz) frequency range, both the N1 response to the standard stimulus and the MMN (that is, the additional response to the deviant stimulus (difference between the red and blue lines)) have primary power within the theta (4–7 Hz) range[46]. Reductions in N1 and MMN thus indicate dysfunction of neural ensembles in the auditory cortex involving GABA neuron subtypes other than the parvalbumin-expressing neurons, which are most associated with the gamma rhythm. **d** | Illustration of the intracranial recording approach in monkeys in which a lamina array electrode is used to sample across cortical layers. The auditory event-related potential (AEP) can be obtained from such recordings. The current source density (CSD) is calculated as the second-spatial derivative of the AEP and distinguishes regions of net inward current flow (current sinks), which represent active depolarization, from regions of net outward current flow (current sources), which represent either active hyperpolarization or passive current return. Generation of the surface MMN occurs coincidently with late activity within superficial cortical layers, suggesting that it is a product of an underlying generator. **e** | Schematic illustration of the MMN response. MMN reflects the increased activity within superficial cortical layers in response to deviant relative to standard stimuli. A proposed underlying mechanism for the MMN is that repetitive standard stimuli disinhibit neurons that are sensitive to different stimulus features (for example, a stimulus of one tonal frequency disinhibits neurons sensitive to other stimulus frequencies), leading to subthreshold depolarization and therefore unblocking of local NMDA receptors (NMDARs). When such neurons are subsequently stimulated, net current flow through open, unblocked NMDARs is larger than if the standard stimuli had not been previously presented[3]. The intracortical administration of an NMDAR antagonist eliminates the differential response to deviant versus standard stimuli, supporting the role of NMDARs in the MMN. **f** | Schematic illustration of the intracortical auditory N1 response. The auditory N1 shows a characteristic refractoriness function, in which the amplitude of N1 decreases progressively as the interstimulus interval (ISI) is decreased from 9 to 0.3 seconds. The reduction in response amplitude reflects progressive inhibition of NMDAR-mediated current flow due to local GABAergic inhibition. Thus, infusion of an NMDAR antagonist (for example, ketamine) into the auditory cortex leads to significant inhibition of local current flow within the auditory cortex. By contrast, infusion of a type A GABA receptor ($GABA_AR$) antagonist, such as bicuculline, leads to significant enhancement of activity. The effects of bicuculline are reversed by administration of an NMDAR antagonist, suggesting that neurons within these layers are under tonic inhibition by local GABAergic interneurons. The top panels of part **b** are adapted with permission from REF. 32, Elsevier. Part **d** is adapted with permission from REF. 166, Elsevier.

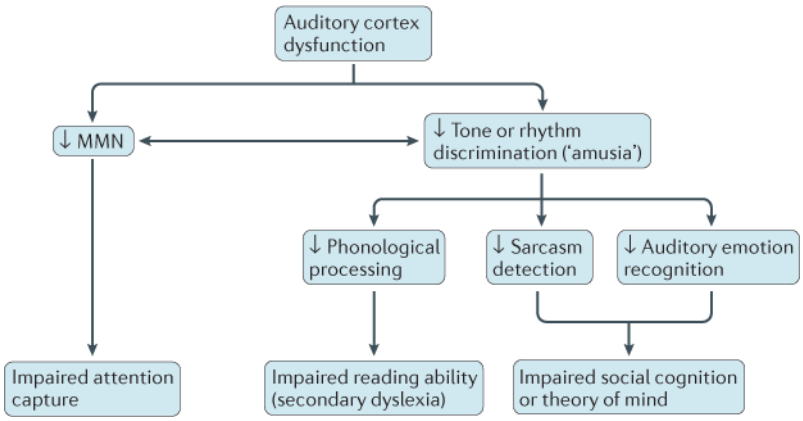

Figure 4. Contributions of auditory sensory dysfunction to higher-order cognitive impairments

Schematic illustration of pathways from auditory sensory cortex dysfunction to impaired psychosocial function in schizophrenia. The ability to detect changes in auditory tone or rhythm is crucial for the detection of alterations in tone of voice (prosody), which communicates information about emotion (for example, whether someone is happy or sad) and/or attitude (for example, sincerity versus sarcasm), which in turn contributes to understanding of another person's mental state ('theory of mind'). Auditory tonal ability is also critical for functions such as 'sounding words out' (that is, phonological processing) during reading. As a result of reduced auditory feature discrimination, individuals with schizophrenia show impairments in processes such as auditory emotion recognition[22,90] and phonological processing[93] that lead to social cognitive and reading impairments, respectively. Mismatch negativity (MMN) is an additional auditory cortical process that is critical for everyday function. MMN reflects the outcome of a screening process, located in the auditory cortex that constantly monitors the environment for potentially relevant alterations in the pattern of background auditory stimulation, even when such events occur outside the focus on conscious attention. In healthy volunteers, generation of MMN within the auditory cortex is linked to subsequent activation of structures such as the insula and the anterior cingulate cortex that are part of the salience network, and to deactivation of visual regions, leading to bottom-up attentional capture. In schizophrenia, these processes are impaired, leading to reduced sensitivity to ongoing environmental (auditory) events[10,94]. Deficits in MMN are highly interrelated to impaired functional outcome in schizophrenia, including impairments in reading[93] and educational achievement[32,167]. As opposed to behavioural measures that may be difficult to translate across species, MMN provides an objective neurophysiological measure that can be implemented in primates and/or rodents to investigate underlying neural mechanisms.

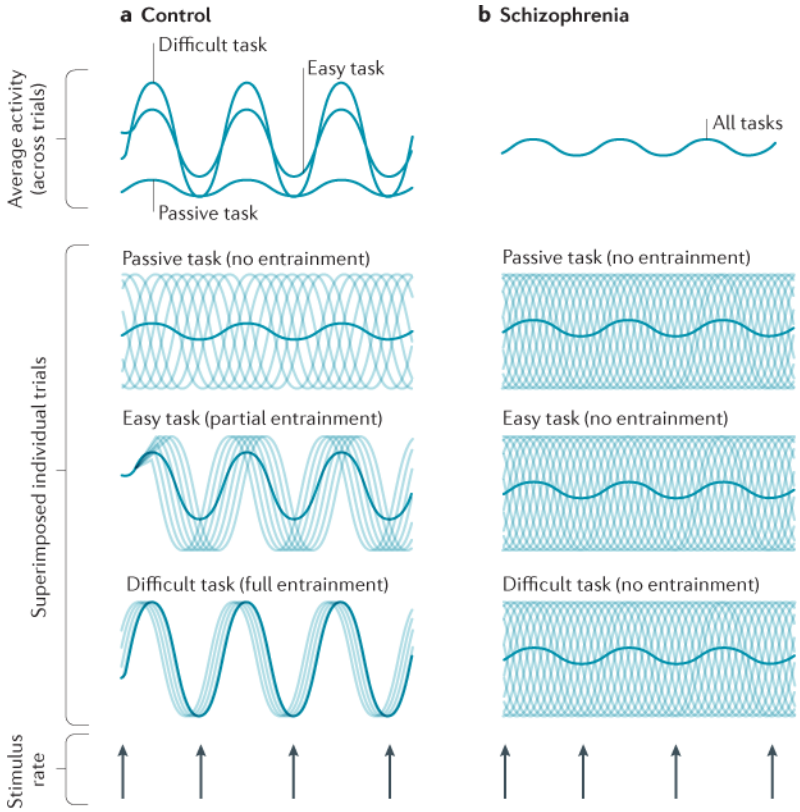

Figure 5. Impaired delta entrainment during auditory processing in schizophrenia

In addition to showing reduced responses to individual auditory stimuli, individuals with schizophrenia also fail to take advantage of the regularity of stimulation rate across stimulus presentation. In most cognitive paradigms, stimuli are presented at regular presentation rates of about 0.25–2 seconds, corresponding to frequencies in the delta range (0.5–4 Hz). The regularity of this rate allows the brain to predict when the next stimulus will be presented in order to optimize use of processing resources. **a** | In healthy controls, the average delta activity across trials increases as the task condition goes from passive auditory stimulation to easy auditory discrimination to difficult discrimination. This change in average response across trials corresponds to a progressive increase in the degree to which individual responses are phase-locked to the stimulus presentation rate. Thus, under passive listening conditions, delta activity is randomly distributed relative to the stimulation rate so that activity averages towards zero across trials. As task difficulty increases, the degree of inter-trial coherence (ITC) increases, leading to reduced cancellation across trials and thus greater average surface activity while performing the task. Individual trial responses are shown schematically in different shades, with the mean response in the darkest shade. **b** | In schizophrenia, no increase in average delta activity is observed across trials, suggesting that stimuli do not effectively reset the phase of the ongoing delta activity even in the difficult task condition. Schematics are based on data from REF. 47.

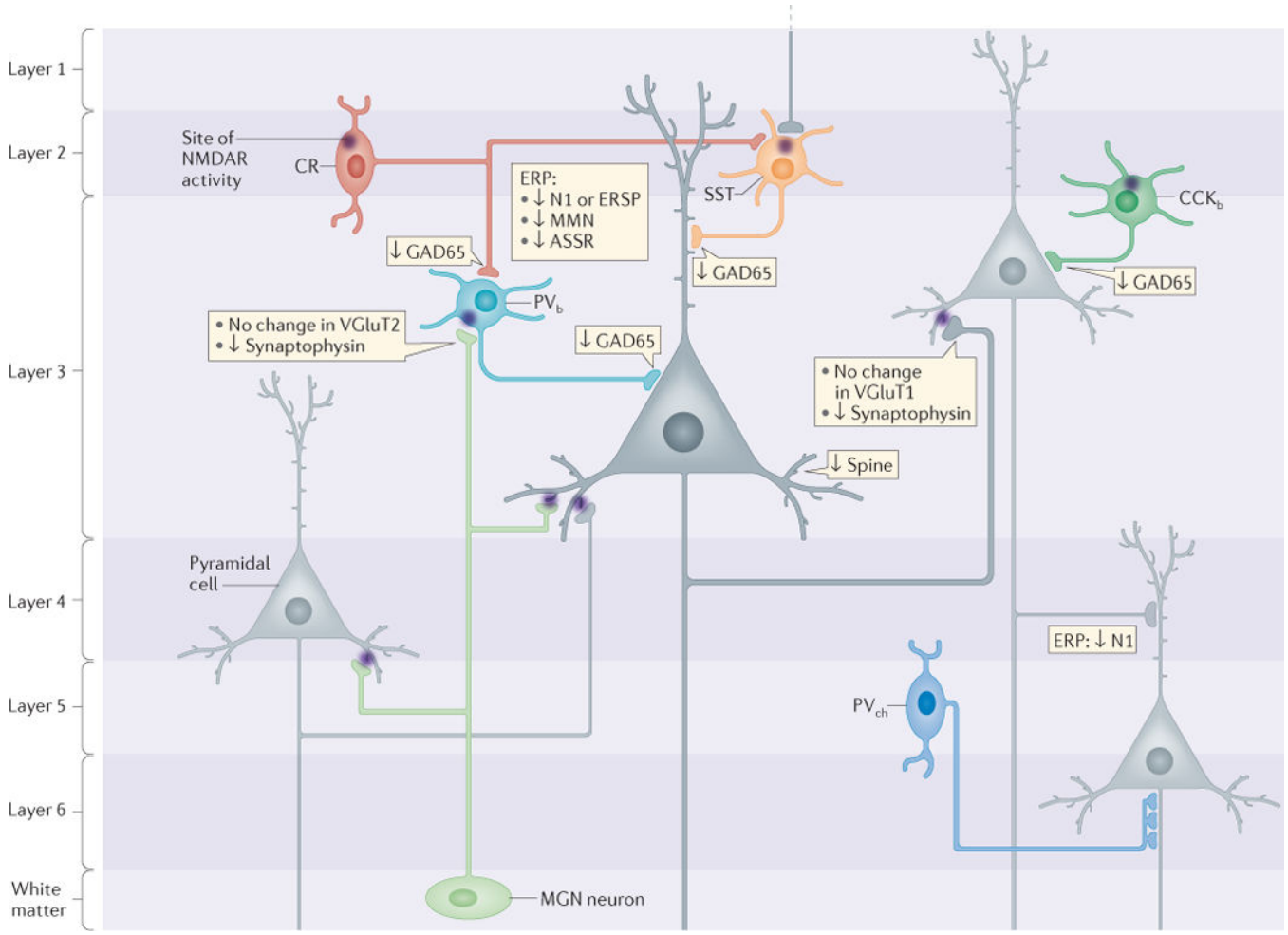

Figure 6. Auditory cortical circuitry: neurophysiological and histological findings in schizophrenia

Illustration showing the convergence between neurophysiological (event-related potential (ERP) and event-related spectral perturbation (ERSP)) and post-mortem findings in schizophrenia. In the auditory cortex, as in other brain regions, GABAergic interneurons can be subdivided by markers such as parvalbumin (PV), cholecystokinin (CCK), somatostatin (SST) and calretinin (CR). Inputs to the cortex arise predominantly from the medial geniculate nucleus (MGN) and form synapses on glutamatergic pyramidal (principal) neurons in layer 4 and lower layer 3. These inputs also synapse onto PV-expressing basket cells (PV_b), which originate local feedback and play a critical part in the generation of local gamma rhythms. Histological findings show that density and expression levels of vesicular glutamate transporter (VGluT) are relatively intact in schizophrenia in terminals of both MGN thalamocortical afferents (VGluT2) and corticocortical glutamatergic synapses (VGluT1), suggesting that the input to the cortex is also relatively intact. However, synaptophysin expression is reduced in deep layer 3, potentially increasing the susceptibility of these inputs to synaptic depression and thereby altering neurophysiological activation patterns. Dendritic spine density is reduced on pyramidal neurons in deep layer 3 of the auditory cortex, potentially owing to impaired NMDA receptor (NMDAR) function and

impaired spine maintenance. Expression of glutamate decarboxylase 65 (GAD65) in terminals of GABA neurons is also reduced in deep layer 3, although whether this affects all or some the GAD65-expressing GABA neuron subtypes is not known. Only PV-expressing chandelier cells (PV_{ch}) do not express GAD65. The putative generator layers for specific neurophysiological components are shown in boxed text. In particular, generators for auditory P1, mismatch negativity (MMN) and auditory steady-state response (ASSR) are localized primarily to supragranular layers, whereas generators for auditory N1 are localized primarily to infragranular layers. In general, electroencephalographic activity recorded from the scalp reflects current flow through glutamatergic and voltage-sensitive ion channels within the dendritic arbors of pyramidal neurons. Dendritic arbors contribute disproportionately to electroencephalographic activity both because of their greater extent relative to axonal arbors and because the low impedance of dendritic (versus axonal) membranes gives rise to large currents that can be detected even at a distance. In addition, the asymmetrical structure of pyramidal neurons (versus interneurons) gives rise to an ‘open-field’ generator configuration that allows neural activity to propagate outside the local ensemble and thus to be detectable with far-field or scalp electrodes. In schizophrenia, the extent of neuronal arbors may be reduced in part due to a reduced number of spines, leading to less membrane surface area and thus to a smaller amplitude ERP. Furthermore, functional impairments of thalamocortical input, possibly due to reduced synaptophysin levels may lead to both reduced amplitude of response to individual stimuli and decreased synchronization across successive trials. Downregulation of PV and GAD65, particularly within PV_b may lead to impaired regulation of high-frequency gamma (30–80 Hz) activity, whereas impaired interaction between SST and pyramidal neurons may be responsible for impaired theta (4–7 Hz) frequency activity, as reflected in impaired auditory N1 and MMN generation. NMDARs are primarily located on pyramidal cell dendrites and GABAergic interneurons, and may thus lead to glutamatergic and GABAergic dysfunction.