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EXPERT REVIEW

What causes aberrant salience in schizophrenia? A role for impaired short-term habituation and the *GRIA1* (GluA1) AMPA receptor subunit

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The *GRIA1* locus, encoding the GluA1 (also known as GluRA or GluR1) AMPA glutamate receptor subunit, shows genome-wide association to schizophrenia. As well as extending the evidence that glutamatergic abnormalities have a key role in the disorder, this finding draws attention to the behavioural phenotype of *Gria1* knockout mice. These mice show deficits in short-term habituation. Importantly, under some conditions the attention being paid to a recently presented neutral stimulus can actually increase rather than decrease (sensitization). We propose that this mouse phenotype represents a cause of aberrant salience and, in turn, that aberrant salience (and the resulting positive symptoms) in schizophrenia may arise, at least in part, from a glutamatergic genetic predisposition and a deficit in short-term habituation. This proposal links an established risk gene with a psychological process central to psychosis and is supported by findings of comparable deficits in short-term habituation in mice lacking the NMDAR receptor subunit *Grin2a* (which also shows association to schizophrenia). As aberrant salience is primarily a dopaminergic phenomenon, the model supports the view that the dopaminergic abnormalities can be downstream of a glutamatergic aetiology. Finally, we suggest that, as illustrated here, the real value of genetically modified mice is not as 'models of schizophrenia' but as experimental tools that can link genomic discoveries with psychological processes and help elucidate the underlying neural mechanisms.

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There is now strong evidence that hyper-dopaminergic activity underlies the positive psychotic symptoms of schizophrenia.[1–3] Dopaminergic abnormalities have a similarly proximate role in aberrant salience,[4,5] which Kapur and others have theorized is central to the genesis and understanding of positive psychotic symptoms.[6–9] However, the cause of this dopamine dysregulation is unspecified in Kapur's model and has not yet been resolved.[8,10] Indeed, while considerable effort has gone into investigating and describing the putative links between dopamine, aberrant salience and psychosis, comparatively little effort has been expended in identifying the possible causes of aberrant salience.

Howes and Kapur[8] noted that although the dysregulated, hyperdopaminergic state could be the result of a primary abnormality in the mesolimbic dopamine system, it could also be a secondary consequence of some other brain disturbance (or disturbances) and thus represent a 'final common pathway' in schizophrenia. The glutamate system is a prime candidate for this upstream abnormality[6,11–15] with diverse evidence for glutamatergic dysfunction, particularly NMDAR signalling, in the pathophysiology of schizophrenia,[16,17] including data from postmortem,[18,19] neuroimaging,[20,21] and immunological[22] studies of the disorder, as well as indirectly from pharmacological findings[17] and animal models.[23] An aetiological role for glutamate is now also likely based on recent genetic data. Initial evidence came from candidate gene association studies[24,25] with observations that genes involved in glutamate synapses and NMDAR-mediated signalling are over-represented among schizophrenia genes.[26–29] These findings were subsequently supported by pathway analyses of genome-wide association studies (GWAS) and by *de novo* copy number variant data[30,31] and exome sequencing.[32]

Extending these data, the Ripke *et al*.[33] GWAS found that a locus upstream of GRIA1 showed significant association to schizophrenia.[33] This association was confirmed by the recent larger GWAS study ($P = 1.06 \times 10^{-10}$), which also identified genome-wide significant association to other glutamate receptor loci, discussed below.[34] *GRIA1* encodes the GluA1 (also known as GluRA or GluR1) subunit of the AMPA subtype of glutamate receptor. This association complements prior evidence that AMPARs, as well as NMDARs, are involved in the disorder.[18,35–40] Of particular relevance here is evidence that there are reductions of GluA1 mRNA[36,37] and GluA1,[35] as well as AMPAR binding sites,[39] in the hippocampus in schizophrenia, and which do not appear to be secondary to antipsychotic medication.[41–44]

In this review, we describe the behavioural phenotype of *Gria1*$^{-/-}$ mice and, in particular, a deficit whereby these mice fail to reduce the amount of attention that is paid to recently presented stimuli.[45,46] This failure to habituate means that stimuli continue to be surprising and grab attention for longer than would be normal. In fact, under some circumstances, these mice actually display sensitization, whereby more attention is paid to a recently presented stimulus than to a non-recent stimulus.[47] Thus for these mice the stimulus is treated as even more salient or

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intense the second time it is presented. Deficits in short-term habituation therefore represent a potential driver of aberrant salience. This provides a key, mechanistic component of our present hypothesis that GluA1 dysfunction contributes to aberrant salience in schizophrenia; we further suggest that this is mediated via enhanced dopamine signalling. This proposal provides a plausible causal link between a robust schizophrenia risk gene locus and a psychological process of central importance in psychosis. Moreover, it directly links the glutamate and dopamine components of the disorder.

ABERRANT SALIENCE, DOPAMINE AND PSYCHOSIS

Psychosis has been viewed as a disorder of aberrant salience,[7] mediated via a hyper-dopaminergic state.[6,7,9,48,49] For our purposes, salience can be defined as the ability of a stimulus to grab attention and to drive behaviour.[5,7] Salience not only reflects the innate properties of the stimulus (for example, brightness, loudness) but can also reflect its potential motivational significance. Kapur[7] suggested that, before experiencing psychosis, patients will develop an exaggerated release of dopamine, independent of, and out of synchrony with, the context. The cause is not specified in Kapur's model, but the resulting hyperdopaminergic state will then lead to the persistent and inappropriate assignment of salience to stimuli.

This state of aberrant salience can lead to inappropriate associations being formed, potentially via abnormal prediction error signals in the ventral striatum and other brain regions.[50–54] For example, Jensen *et al*.[50] demonstrated aberrant learning and ventral striatal activation in schizophrenia using an aversive, Pavlovian discriminative fear conditioning paradigm. In this task, subjects were exposed to different visual stimuli. One stimulus (the conditioned stimulus; CS+) was paired with a loud noise (the unconditioned stimulus), whereas the other visual stimulus was not paired with the aversive event (CS−). Jensen and colleagues found inappropriately strong ventral striatal activation in response to the control stimulus (CS− cue), accompanied by abnormal learning, assessed both by self-report and galvanic skin responses (see also Holt *et al*.[55]). Similarly, Murray *et al*.[52] found that first-episode patients with active positive symptoms responded faster to neutral stimuli than controls during a reward learning task (response latencies were not significantly different to rewarded stimuli) and that these subjects exhibited abnormal BOLD responses associated with reward prediction error in dopaminergic midbrain, striatum and limbic areas. Likewise, Roiser *et al*.[56] have reported aberrant reward learning in symptomatic but not asymptomatic patients with schizophrenia, and in unmedicated individuals at ultra-high risk of developing the condition.[57] This aberrant reward learning was correlated with the severity of delusion-like symptoms, as were ventral striatal BOLD responses to irrelevant stimuli.

Thus it has been widely argued that the psychotic symptoms associated with schizophrenia, such as delusions and hallucinations, are the result of this fundamental abnormality in learning[7,54,58,59] and that their occurrence is correlated with aberrant salience.[56] Kapur hypothesized that patients would begin by assigning significance or importance to an incidental, neutral stimulus and, over a period of time, build up a complex delusion as a way of explaining why this unimportant object or detail has taken on such great meaning. Delusions are therefore a 'cognitive effort by the patient to make sense of these aberrantly salient experiences'[7] and they reflect a maladaptive update of the patient's world view.[53] Similarly, hallucinations may be experiences that result from aberrant salience being applied to internally generated stimuli.

Kapur's ideas build on the incentive or motivational salience hypothesis of dopamine's actions put forward by Berridge and Robinson,[60] Robbins and Everitt[61] and others.[62–67] Kapur suggested that the mesolimbic dopamine system underlies motivational salience and so 'mediates the conversion of the neural representation of an external stimulus from a neutral, cold bit of information into an attractive or aversive entity' (that is, something that is of biological significance).[7] In addition, dopamine can facilitate aspects of associative learning (for example, refs. 68–71). Therefore, the ability of a stimulus to grab attention, drive action and potentially form associations with other stimuli are all influenced by dopamine.

DOPAMINE AND NOVELTY

The hypothesis that dopamine underlies the incentive or motivational salience of stimuli (and hence provides a signal of biological significance) captures a key element of what dopamine is doing, but it may not be the whole story: dopamine release is also associated with novelty. Although burst firing of dopamine cells in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) is increased by unexpected rewards, and reduced if an expected reward is omitted, crucially dopamine neuronal activity is also triggered by novel stimuli that are not yet, and may never be, directly associated with reward or punishment and are affectively neutral. Human functional magnetic resonance imaging (fMRI) studies have demonstrated that activation of the VTA/SNc can code for the absolute novelty of a stimulus and that this haemodynamic signal exhibits repetition suppression with repeated presentation of the stimulus.[72] More directly, putative dopamine neurons in the VTA/SNc have been found to exhibit an increase in firing to novel, neutral stimuli.[73–75] Furthermore, recent evidence using dopamine voltammetry directly shows increased dopamine release in ventral striatum in response to novel, neutral stimuli.[69,76–78] The response to novelty may not be restricted to just the mesolimbic VTA-ventral striatal pathway but may also include activity in the SNc–dorsal striatal circuitry.[72,79] Thus, dopamine release in the striatum is associated not only with incentive or motivational salience but also with novelty. As such, dopamine may signal not only stimuli of biological significance but also stimuli of 'potential' biological significance (as would be the case for any novel stimulus). Indeed, it has been argued that the coding of absolute novelty by dopamine may be treated like a signal that motivates exploration for potential reinforcers.[72,80]

A key point is that when stimuli are novel they grab the focus of attention and are perceived more intensely. Novel stimuli generate exploration,[81] and they readily enter into associations with other stimuli.[82] Therefore, novelty is important, both in terms of determining salience, as well as for the corresponding changes in dopamine activity.[5] Glutamate receptors, and in particular GluA1-containing AMPARs, have a fundamental role in the response to novel stimuli and in the short-term habituation to such stimuli as a result of recent experience.[45,46]

Gria1 (GluA1) KNOCKOUT MICE: SELECTIVE IMPAIRMENTS IN SHORT-TERM HABITUATION

The AMPAR is a hetero-oligomeric protein complex consisting of combinations of four subunits (GluA1–4, or GluRA–D), each encoded by a separate gene (*GRIA1–4)*.[83] Mice in which the gene encoding GluA1 is knocked out constitutively exhibit normal development, life expectancy and fine structure of neuronal dendrites and synapses (*Gria1*$^{-/-}$ mice[84]). However, there is a reduction in the number of functional AMPA receptors, and both somatic and synaptic glutamatergic currents are reduced.[85–87] A number of studies have shown deficient long-term potentiation in hippocampal slices from *Gria1*$^{-/-}$ mice,[84–86] although more recent studies have indicated that GluA1 subunits may contribute primarily to short-lasting forms of synaptic plasticity.[87–89]

Behaviourally, *Gria1*$^{-/-}$ mice are indistinguishable from wild-type littermates in their home cage environment. However, closer

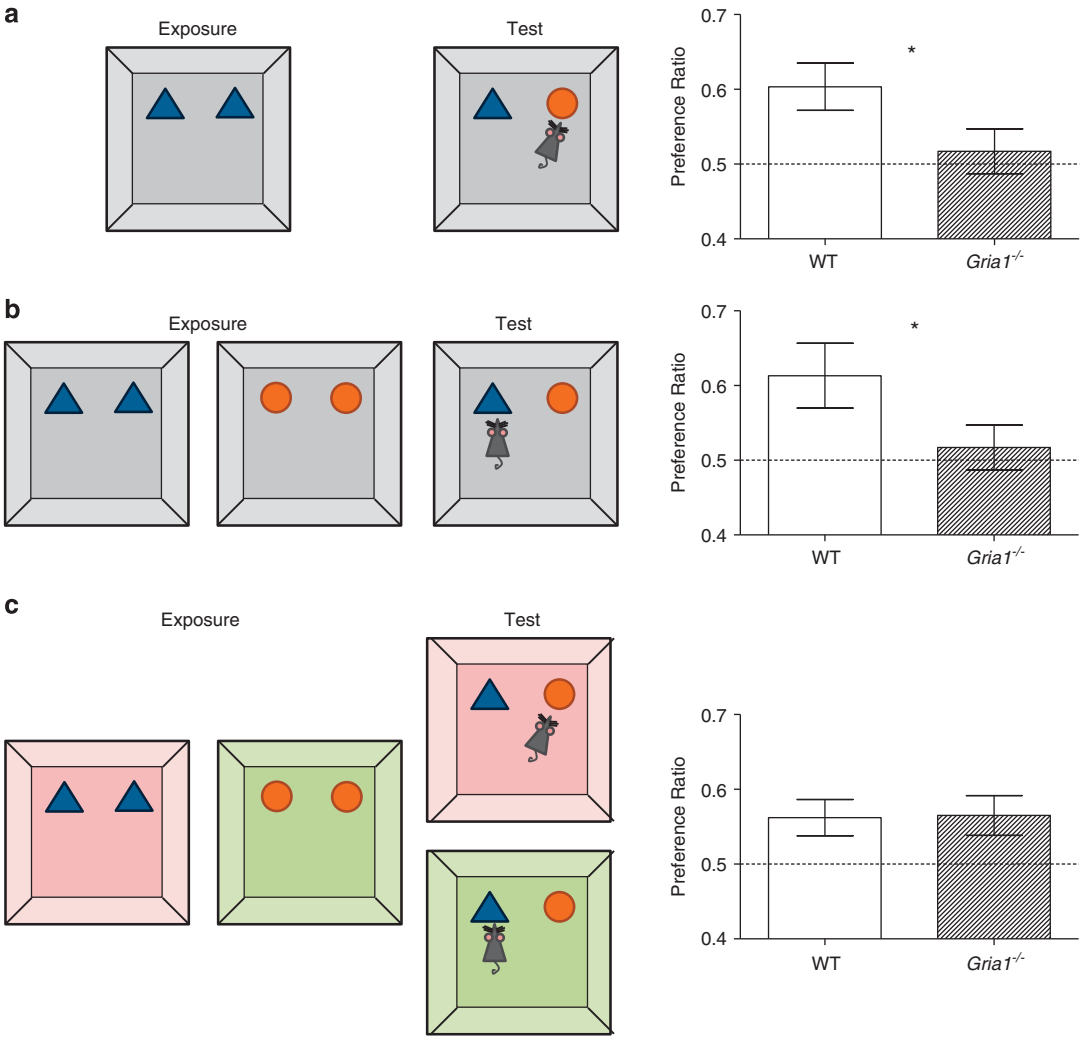

Figure 1. *Gria1*$^{-/-}$ mice display impaired short-term habituation on the novel object recognition test. (**a**) The top left panel shows the design of the standard novel object recognition task. In the Exposure phase (10-min duration), wild-type (WT) mice were exposed to two copies of an object, and then after a 2-min interval they received a 5-min Test in which they were allowed to explore a duplicate of the familiar object and a novel object. The levels of object exploration for *Gria1*$^{-/-}$ mice for both exposure and test phases were yoked to WT mice. The times spent exploring the novel object during the test phase are shown as a ratio of the total time spent exploring both objects. The dashed line at 0.5 indicates chance performance. *Gria1* deletion impaired memory on the standard object recognition task (right panel). Error bars indicate ±s.e.m. (**b**) The middle panel shows the design of the object recency task. In the Exposure phase, WT mice received two 10-min exposures to two different objects separated by a 2-min interval. The Test phase (5-min duration) commenced 2 min after the last exposure. Mice were allowed to explore the more recently and the less recently presented objects. The levels of object exploration for *Gria1*$^{-/-}$ mice for both exposure and test phases were yoked to WT mice. The times spent exploring the less recently experienced object are shown as a ratio of the total time spent exploring both objects. The dashed line at 0.5 indicates chance performance. *Gria1* deletion impaired memory on the object recency test (right panel). Error bars indicate ±s.e.m. (**c**) The bottom panel shows the design of the context-dependent object recognition task. In the Exposure phase, two different objects were exposed in two different contexts. WT mice received four 10-min exposures to each object, one per day for 4 days. On the fifth day, mice were simultaneously exposed to both objects in both of the contexts in two 5-min Tests. The levels of object exploration for *Gria1*$^{-/-}$ mice for both exposure and test phases were yoked to WT mice. The times spent exploring the object not previously paired with the test context (that is, the unpaired object) are shown as a ratio of the total time spent exploring both objects. The dashed line at 0.5 indicates chance performance. *Gria1* deletion did not impair context-dependent object recognition task (right panel). Error bars indicate ±s.e.m. (Data from Sanderson *et al.*[93]). *$P < 0.05$ difference between groups.

inspection in experimental settings reveals a specific but striking impairment in short-term habituation in these animals. Habituation is the decline in the tendency to respond to a stimulus that has become familiar due to prior exposure. This is likely to be an adaptive response to ensure that attentional resources are allocated to novel and potentially important stimuli. It has been argued that habituation can be fractionated into short- and long-term processes, with different underlying psychological and neural mechanisms.[45,90–92] *Gria1*$^{-/-}$ mice exhibit a pronounced deficit in short-term habituation. For example, on the novel object recognition test, *Gria1*$^{-/-}$ mice are slower to habituate to a would-be familiar object (Figure 1). In this task, mice are first typically exposed to two identical copies of an object during a sample ('Exposure') phase and allowed to explore freely. When a wild-type animal is presented with novel objects, it will begin to explore them, but its exploratory activity gradually decreases or habituates as the objects become familiar. In a subsequent 'Test' phase (usually conducted after a short delay), the mouse is exposed to a further copy of the original object (now familiar) and a novel object. Wild-type animals will preferentially choose to explore the

novel alternative, reflecting their stimulus-specific habituation to the original object. In contrast, *Gria1*$^{-/-}$ mice display a deficit in short-term habituation:[93] they fail to reduce the amount of attention that is paid to recently presented stimuli. Consequently, *Gria1*$^{-/-}$ mice show less preference than wild-type mice for a novel object compared with a familiar object that was presented recently[93] (Figure 1a). *Gria1*$^{-/-}$ mice are also impaired on a recency-dependent version of the object recognition task[93] (Figure 1b). However, *Gria1*$^{-/-}$ mice can recognize an object as familiar when it is consistently and repeatedly presented in a given, distinctive context (the object-in-context paradigm;[93] Figure 1c). This reflects the fact that they can use the context or place to associatively retrieve or prime the memory of that object from long-term memory, such that it feels familiar (that is, long-term habituation is preserved). Importantly, this also shows that their deficit in short-term habituation is neither a basic perceptual problem nor a global memory deficit.

The short-term habituation deficit can also be demonstrated using a simple, spatial novelty preference task, during which animals spontaneously explore a Perspex Y-maze surrounded by extra-maze spatial cues (Figure 2; Sanderson *et al*.[94,95]). During the sample or 'Exposure' phase, the animals are allowed to explore two arms of the maze, while access to the third arm is blocked off. During the subsequent choice phase, all three arms of the maze are available to be explored. Wild-type mice avoid the recently visited, familiar arms and choose to explore the novel arm. In contrast, *Gria1*$^{-/-}$ mice fail to habituate to the recently visited spatial locations and therefore show no preference between the novel and familiar arms. This short-term spatial memory deficit is in marked contrast to the normal, or even enhanced, long-term associative spatial reference memory that *Gria1*$^{-/-}$ mice exhibit on tasks like the water maze or radial maze,[84,94,96–98] again demonstrating that their short-term habituation deficit is not due to perceptual impairments or a global memory deficit.

Thus *Gria1*$^{-/-}$ mice are slower to habituate to both spatial and non-spatial stimuli and, as a consequence, treat stimuli as novel and salient for longer than wild-type mice. They are unable to filter out, and reduce attention to, recently experienced stimuli. This habituation deficit or attentional gating failure in *Gria1*$^{-/-}$ mice may also explain their deficit in prepulse inhibition, albeit the failure to habituate in the latter setting manifests over a different timescale.[99]

GRIA1 KNOCKOUT MICE EXHIBIT SENSITIZATION

Notably, under some circumstances, salience actually increases with repeated or continued exposure to a stimulus in *Gria1*$^{-/-}$ mice. This is called sensitization. For example, in a recent experiment we measured how much time mice spent looking at different light stimuli in an operant box, depending on their recent experience (Figure 3; Sanderson *et al*.[47]). Mice either received two exposures to the same light separated by 30 s (for example, flashing light followed by flashing light) or received a pairing consisting of two different light stimuli (for example, flashing light followed by a constant light), again separated by 30 s. In both wild-type and *Gria1*$^{-/-}$ mice, if the two light stimuli in the sequence were different then animals spent an equal amount of time looking at both lights. In contrast, if the two light stimuli were the same then wild-type mice spent less time looking at the light on its second presentation, reflecting short-term habituation to the light. However, when the same light was presented twice to *Gria1*$^{-/-}$ mice they actually spent more time attending to the light on its second exposure (relative to the first presentation of that light, and relative to the presentation of a different light that had not been presented recently). Therefore *Gria1*$^{-/-}$ mice do have a memory of the specific light stimulus that they have just experienced (their behaviour is altered by that recent prior exposure). However, they express that memory in a very different way, attending more to the recently presented light compared with a more novel light. Thus for *Gria1*$^{-/-}$ mice a recently presented stimulus can generate exaggerated (and hence aberrant) salience, in the absence of any evidence for its motivational significance.

Importantly, this attentional deficit in *Gria1*$^{-/-}$ mice is set against an intact ability to form associations between stimuli. Associative learning is not impaired in these animals in a variety of experimental settings, including both maze and operant tasks, and in both spatial and non-spatial paradigms.[84,96,97,100] Indeed, in some situations *Gria1*$^{-/-}$ mice may actually form associations more readily than their wild-type controls.[97,101,102] This potentially reflects the fact that *Gria1*$^{-/-}$ mice, by finding a given stimulus more salient, and by paying more attention to that stimulus, are more likely to associate other events or consequences (such as reward) with its presence, thus facilitating long-term memory formation.

Notably, we have also shown that *Gria1*$^{-/-}$ mice can exhibit long-term memory under conditions where there is no evidence of long-term memory in wild-type controls.[94] Thus, in this instance *Gria1*$^{-/-}$ mice could be said to demonstrate 'inappropriate' learning (where 'inappropriate' learning is defined as learning that isn't exhibited by control subjects). An extension of this is the prediction that these mice will also display abnormalities in credit assignment (that is, the forming of inappropriate associations between stimuli and events in a complex, temporally dynamic environment in which there are multiple cues competing for associative strength), leading to false inferences. This would provide a further demonstration of the kind of aberrant learning

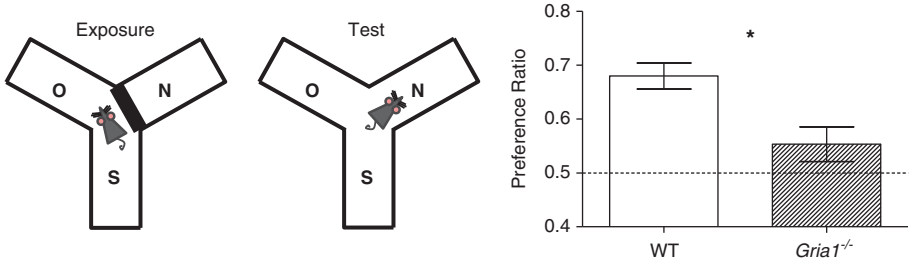

Figure 2. *Gria1*$^{-/-}$ mice display impaired short-term habituation on the spatial novelty preference test. During a 5-min Exposure phase (left panel), mice were allowed to explore two arms (Start and Other) of a 3-arm, Perspex Y-maze surrounded by distal extra-maze cues. After a 1-min delay, the mice were returned to the maze for the Test phase (2-min duration), during which they were now able to explore freely all three maze arms, including the previously unvisited (novel) arm (centre panel). *Gria1* deletion impaired performance on the spatial novelty preference test. Wild-type (WT) mice exhibit a preference for the previously unvisited (Novel) arm over the two familiar arms to which they have previously been exposed (Start and Other). *Gria1*$^{-/-}$ mice did not show a significant preference for the novel arm. Ratio of time spent in the novel versus other arm (±s.e.m.). (Data from Sanderson *et al*.[95]). *$P < 0.05$ difference between groups.

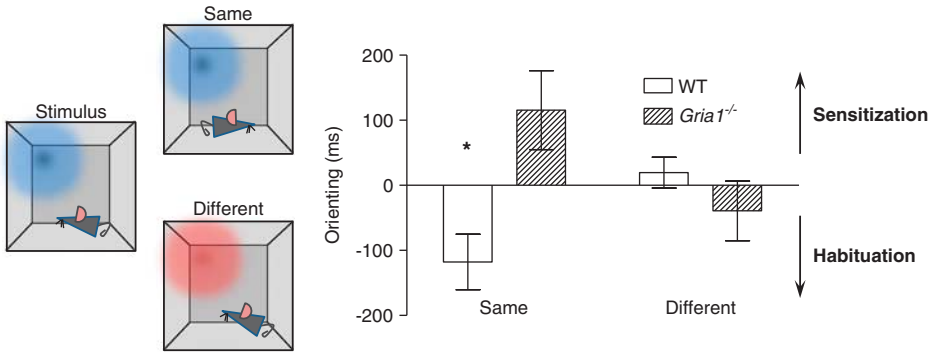

Figure 3. *Gria1*$^{-/-}$ mice display increased attention (sensitization) to a recently experienced light stimulus. Unconditioned suppression of magazine responding to visual stimuli in an operant chamber was used as an indirect measure of the orienting response. Mice were exposed to pairs of light stimuli. Each stimulus in the pair was presented 30 s apart (for example, flashing vs constant light, depicted graphically as red vs blue; left panel). For half of trials, the first light in the pair was the same as the second (Same condition). For the remaining trials, the first light was different from the second (Different condition). Orienting to the first light in the pair was subtracted from orienting to the second light to give a difference score (Orienting; ms). In the Same condition, wild-type (WT) mice exhibited a reduced orienting response to the second stimulus in the pair. In contrast, *Gria1*$^{-/-}$ mice exhibited greater responding to the second stimulus. Both groups showed similar levels of orienting to both stimuli in the pair in the Different condition. This demonstrates that the reduction in orienting in WT mice and the increase in orienting in *Gria1*$^{-/-}$ mice in the Same conditions are stimulus-specific (Data from Sanderson *et al*.[47]). *$P < 0.05$ difference between groups in the Same condition.

that might underlie psychotic symptoms such as delusions, and will be an important further test of our hypothesis in *Gria1*$^{-/-}$ mice.

HABITUATION, SALIENCE AND SCHIZOPHRENIA

How relevant is this short-term habituation deficit in *Gria1*$^{-/-}$ mice to schizophrenia? In his original descriptions, Bleuler[103] presciently noted that patients often experienced 'an absence of the feeling of familiarity'. Subsequently, it has been well documented that patients with schizophrenia exhibit habituation deficits over a range of timescales,[104] both behaviourally (for example, in terms of habituation of the startle response[105–108]) and also physiologically (for example, the reduction in evoked responses to auditory stimuli with repeated presentations[109]). Impairments in prepulse inhibition could also be considered as a failure to reduce the attention paid to a stimulus (the startle stimulus) based on recent prior experience (the prepulse[106,108,110]). Therefore, the link between habituation deficits and schizophrenia has been made before. What is novel here is the link between deficits in short-term habituation that can lead to sensitization and the notion that patients may experience aberrant salience, with greater attention being paid to recently presented stimuli. Indeed, it is tempting to draw parallels between the exaggerated (aberrant) salience experienced by *Gria1*$^{-/-}$ mice and the attentional abnormalities reported in schizophrenia, including during the prodrome. Kapur[7] noted that patients experience a stage of heightened sensory or perceptual awareness during the prodromal phase. Although accounts are usually anecdotal and/or *post-hoc*, they do suggest that everything the person experiences is intense, interesting, and highly salient. For example, patients report feelings, such as 'I developed a greater awareness of…My senses were sharpened…I became fascinated by the little insignificant things around me…Sights and sounds possessed a keenness that he had never experienced before…It was as if part of my brain awoke which had been dormant…My senses seemed alive….Things seemed clearcut, I noticed things I had never noticed before…My capacities for aesthetic appreciation and heightened sensory receptiveness were very keen at this time. I had had the same intensity of experience at other times when I was normal, but such periods were not sustained for long…' (taken from Kapur[7]).

In essence, people with schizophrenia appear to pay elevated levels of attention to certain stimuli in their environment, in much the same way that the *Gria1*$^{-/-}$ mice pay an increased amount of attention to the recently presented light stimulus in our operant experiment (see Figure 3; Sanderson *et al*.[47]). The fact that these feelings of heightened awareness and intensity of perceptual experience often emerge during the prodrome is consistent with the possibility that these attentional deficits may be a contributory cause of psychosis and could provide the trigger for subsequent positive symptoms.[6,8,111] We suggest that sensitization in *Gria1*$^{-/-}$ mice is homologous to the heightened intensity of sensory stimulation experienced by patients during the prodromal phase of the disorder.

PSYCHOLOGICAL AND NEURAL MECHANISMS UNDERLYING SHORT-TERM HABITUATION AND THEIR ALTERATION IN SCHIZOPHRENIA

How do deficits in short-term habituation result in sensitization, and how might these attentional phenomena be represented in the brain? Short-term habituation reflects a component of short-term memory that results in less attention being paid to a recently experienced stimulus (the stimulus might be said to exist in a secondary or reduced state of attention). This is distinct from an active form of short-term memory that underlies human working memory performance (for example, on N-back or digit span tasks) in which the stimulus representation is actively maintained at the forefront of attention (the primary state of attention). These different short-term memory states therefore map onto different attentional states, reflecting the different amounts of attention being paid to a stimulus.

Wagner[91] proposed a theoretical and computational model of stimulus processing that can explain the relationship between attention, habituation and learning (Figure 4). These ideas are of fundamental importance for understanding how deficits in short-term habituation could lead to aberrant salience and the genesis of psychosis. Wagner suggested that each stimulus is represented by a set of elements. Individual elements can exist in any one of three different activity or attentional states: an inactive state (I), the primary state of attention (A1), or the secondary state of attention (A2). Although proportions of elements for a given stimulus can be in different activity states, individual elements can

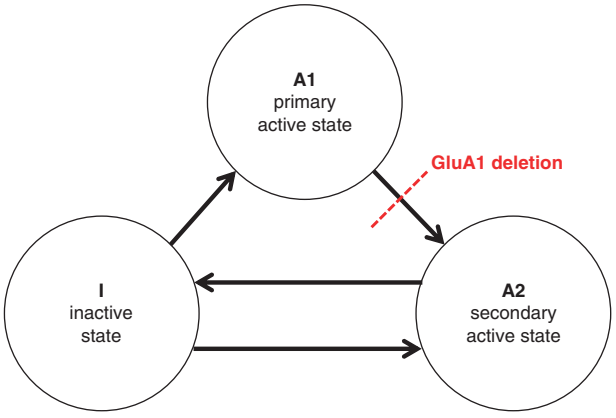

Figure 4. Wagner's model of stimulus processing. Wagner proposed that each stimulus is represented by a number of elements. When a stimulus is presented, a proportion of these elements go from being inactive (I state) and enter into a primary activity or attentional state, which might be considered as the forefront of attention or active short-term memory (A1 state). Elements then rapidly decay from this A1 state into a secondary activity state (A2 state) where they remain before gradually decaying back to the inactive state (I state). Stimulus elements can also go directly from the inactive state to the A2 state (which involves an associative retrieval process based on previously formed long-term memories). This is the basis of long-term habituation and is GluA1-independent; see upper horizontal arrow between I state and A2 state). When the elements of the stimulus are in the A1 state, higher levels of attention are paid to the stimulus, and it can generate strong levels of responding. Also, associations can form between elements of different stimuli that are concurrently active in the A1 state. In contrast, when elements are in the secondary, attentional or A2 state, relatively less attention is paid to the stimulus and it will generate weaker levels of responding. GluA1 deletion retards the transition of elements from the A1 state to the A2 state. This can potentially lead to their accumulation in the A1 state and hence to sensitization. For further details, see text and Sanderson *et al*.[93,94]

only be in one state at any one time. When a stimulus is novel and surprising, it occupies the forefront of attention, is highly salient and generates strong levels of responding. This corresponds to the stimulus elements being in the A1 state. Also, associations can form between elements of different stimuli that are concurrently active in the A1 state. Conversely, when the stimulus is treated as familiar, less attention is paid to the stimulus, and it is less able to enter into associations with other stimuli (that is, associative memory formation will be weaker). This reflects the fact that the stimulus elements are in the secondary attentional (A2) state.

Wagner's model posits that there are two distinct forms of habituation (short-term and long-term habituation), each supported by a separate psychological mechanism. For the purposes of this review, we will concentrate on short-term habituation, which reflects the recent presentation of the stimulus and which is dependent on the GluA1 subunit. When the stimulus is first presented, a proportion of elements go from being inactive (I state) and enter into the primary activity state (A1 state). Elements then rapidly decay from this A1 state into the A2 state, where they remain before gradually decaying back to the inactive I state. If elements are already in the A2 state when the stimulus is presented (for example, during the second presentation of the same stimulus after a short interval), these elements are unable to return directly to the A1 state. As a result, there are fewer stimulus elements available for activation into the A1 state, and consequently less responding to the stimulus (that is, there will be habituation). Thus habitation occurs to the degree to which the stimulus elements are in the A2 state. After sufficient passage of time, the stimulus elements decay back to the inactive state, and so are once again fully available for subsequent activation into the primary A1 state. Therefore habituation is now no longer evident (that is, it is short-lasting).

As described above, *Gria1*$^{-/-}$ mice demonstrate that short-term habituation is GluA1 dependent. In terms of Wagner's model, *Gria1* deletion retards the normal transition of a stimulus representation from A1 to A2 (Figure 4). Hence, in *Gria1*$^{-/-}$ mice stimuli stay at the forefront of attention (that is, in the A1 state) and remain salient for longer than in wild-type mice. In fact, as we have seen, in *Gria1*$^{-/-}$ mice the stimulus can actually be treated as increasingly salient with its repeated or continued presentation, as the elements that comprise the stimulus gradually accumulate in the forefront of attention and are less able to exit to the secondary attentional state.[47] This therefore provides an account of how deficits in short-term habituation can lead to sensitization and gives us important clues as to possible underlying neural substrates.

What are the neural mechanisms that might underlie these changes in attention? We have suggested elsewhere that Wagner's elements could correspond to the neurons that underlie the representation of the stimulus.[46] When a stimulus is first presented and occupies the forefront of attention, a proportion of the neurons in the brain that represent that stimulus will fire and generate action potentials (this would correspond to the primary state of activity). Notably, only when the stimulus elements are in this A1 state can they form excitatory associations with elements of other stimuli, consistent with Hebb's postulate that neurons that fire together wire together.[112–114] In contrast, the secondary state of attention, which corresponds to habituation, presumably reflects the fact that the neurons that represent the stimulus are now less excitable and less likely to fire than when the stimulus was at the forefront of attention, and they are thus also less likely to form associations with neurons representing other stimuli. This transition from the primary to secondary state of attention likely reflects a short-term plasticity process, which depends on *Gria1*, although the precise neural circuits and synaptic mechanisms involved remain to be established (see Sandeson *et al*.[46] for discussion).

Evidence for reduced neuronal activity with repeated presentation of the same stimulus can be found with the phenomenon of repetition suppression of the haemodynamic BOLD signal, which is often observed in human fMRI experiments and in a variety of different brain regions.[72,115–120] Repetition suppression occurs when a recently presented (and now familiar) stimulus is presented again.[115] This reduction in the BOLD response likely reflects the tuning or modulation of neuronal representations such that familiar stimuli activate fewer neurons and evoke less neuronal firing. Consistent with this possibility, single cell recordings show that repetition suppression is associated with a decrease in neuronal firing, at least in some brain regions.[118,120,121]

Notably, Holt *et al*.[104] showed that repetition suppression is impaired in schizophrenia. They showed that, in healthy individuals, medial temporal lobe activity (and in particular hippocampal activity) habituates rapidly with repeated presentations of fearful faces. In contrast, patients exhibited no suppression of BOLD activity, consistent with a failure to habituate. Crucially, there is also evidence suggestive of sensitization in patients. A positron emission tomography imaging study, conducted while subjects performed a passive viewing task,[122] found repetition suppression of cerebral blood flow in the right hemisphere of normal individuals across presentations of the same visual image as expected, but in patients with schizophrenia the blood flow response to the visual stimulus actually increased across the session (the equivalent of repetition enhancement in fMRI[115]). Therefore patients with schizophrenia fail to reduce neuronal activity with repeated presentations of the same stimulus, consistent with their inability to reduce the amount of attention

that is paid to a recently presented stimulus. In some situations, neuronal activity in patients may even increase with repeated presentations of the same stimulus,[122] potentially consistent with sensitization to a given stimulus.

DOPAMINE AS A MEDIATING TRANSMITTER SYSTEM

We have drawn attention to the parallels between the impaired short-term habituation seen in *Gria1*$^{-/-}$ mice and in people with schizophrenia and suggest that these impairments may lead to aberrant salience. We now consider how these processes are linked and the central role that dopamine has.

Given that (i) novelty evokes activity in the striatal dopamine system, coupled with (ii) the short-term habituation deficit and sensitization seen in *Gria1*$^{-/-}$ mice, this leads to the prediction of enhanced dopamine activity in these mice. It is important to point out that this hyper-dopaminergic response would likely be both stimulus-driven and stimulus-specific and therefore not necessarily reflected in baseline measures of the dopamine system. Indeed, tissue levels of striatal dopamine appear normal.[123] However, *Gria1*$^{-/-}$ mice do exhibit a marked locomotor hyperactivity when placed in a novel environment, very reminiscent of the effects of low-dose amphetamine.[99,124] In both cases, animals can exhibit levels of locomotor activity well in excess of the activity levels displayed by controls, consistent with the possibility of sensitization (for example, Wiedholz *et al*.[99]). Furthermore, this hyperactivity is blocked by the dopamine D2 receptor antagonist haloperidol.[99] Using high-speed chronoamperometric measurements of extracellular fluid dopamine levels in anaesthetized animals, Wiedholz *et al*.,[99] found that the velocity of striatal dopamine clearance was slower in *Gria1*$^{-/-}$ mice. This would be predicted to lead to an increase in the magnitude and duration of striatal dopamine responses. Taken together, these results are consistent with a putative hyper-dopaminergic phenotype in *Gria1*$^{-/-}$ mice. To test this prediction explicitly, it will be important to assess dopamine transients in response to novel and recently presented stimuli in freely moving, behaving mice, using techniques like fast-scan cyclic voltammetry,[77,125] to determine what role mesolimbic and nigrostriatal dopamine pathways have in these attentional processes (for example, Totah *et al*.[126]), and, more specifically, whether changes in the novelty/familiarity of stimuli are reflected differently in dopamine signals in wild-type and *Gria1*$^{-/-}$ mice.

It is worth pointing out that current antipsychotic drugs appear to dampen all salience, not just aberrant salience[7,58] (that is, their effects are not stimulus-specific), and they do not rescue deficits in habituation or its physiological correlates.[104–106,109,122] Thus these drugs may effectively silence the problem without correcting the underlying impairment. The analogy might be with a broken radio that is giving out white noise. Turning down the volume will remove the immediate problem (and the distress which it causes) but will not fix the underlying malfunction. Therefore identifying the molecular, synaptic and circuit mechanisms that support short-term habituation may have important therapeutic implications by allowing more targeted suppression of aberrant salience.

GRIA1 AND SCHIZOPHRENIA—THE BROADER CONTEXT

To summarize, studies in *Gria1*$^{-/-}$ mice show that the GluA1 AMPAR subunit has a key role in short-term habituation. *Gria1*$^{-/-}$ mice can pay even more attention to a recently experienced stimulus compared with a more novel stimulus. This phenotype may be of particular interest with regard to psychosis. First, because stimuli are perceived more intensely and/or remain at the forefront of attention for longer, we propose that this short-term habituation deficit can underlie aberrant salience, a process believed to be of central importance in the origin of positive psychotic symptoms. As a consequence, these stimuli are more likely to enter into inappropriate or aberrant associations, leading to the formation of delusions. Thus we suggest that changes in stimulus processing (and the allocation of attention) caused by GluA1 deletion are an upstream cause of deficits in prediction error learning that are seen in patients. Of course, these delusions are often sustained for long periods of time and are impervious to contradictory evidence. Corlett *et al*.[54,127] have likened this tenacity of delusions to the formation of instrumental habits seen in learning experiments with over-training. In this respect, it is worth noting that *Gria1*$^{-/-}$ mice also display an increased propensity for habitual behaviour.[128,129] Further experiments are required to determine whether this is related to the deficits in short-term habituation and its possible consequences for rates of associative learning, or whether it reflects a role for GluA1 in other neural circuits supporting goal-directed behaviour. Second, as the *GRIA1* locus shows genetic association to schizophrenia, these considerations take on possible aetiological significance. They also support the widely held view that dopaminergic changes in schizophrenia are downstream of an abnormality in the glutamate system.[8,10,12,14–16,24,26,29,130]

With regard to the plausibility of these suggestions, several issues regarding the genetics and pathogenesis of schizophrenia are relevant. First, genetic evidence for *GRIA1* involvement in the disorder is far from complete. The GWAS data show association to a locus that is upstream of the gene, and it remains to be proven whether risk single-nucleotide polymorphism(s) within the locus do in fact impact on the biology of GRIA1 (and not, for example, on another gene in the vicinity). It is not a trivial process to move from a genetic association signal to the identification of the molecular consequences of the risk variation,[131–133] as illustrated by investigations of other psychosis genes.[134–136] And, even assuming that *GRIA1* is the target, the effect of the risk variation will likely be subtle, for example, by modulating transcriptional regulation, and possibly contributing to the modest reduction of hippocampal GluA1 expression seen in schizophrenia.[35–37] In this context, the inherent limitations of a constitutive knockout (which models a null mutation or gene deletion) in mouse models relevant to schizophrenia are apparent[137–139] and indicate the value of using additional genetic models of *GRIA1*. Indeed, it is already clear that it may not be necessary to remove all GluA1 subunits to produce the phenotype described here, as behavioural deficits indicative of impaired short-term habituation are also seen in mice in which *Gria1* is knocked out selectively in the parvalbumin-positive (PV+) population of interneurons.[140] Furthermore, mice in which NMDARs have been ablated selectively from PV+ cells, or mice in which PV+ cell output has been silenced, display arguably similar phenotypes.[141–144] Hippocampal PV+ interneurons may be particularly important for these behavioural phenotypes,[145] in line with a key role for this brain region in regulating attentional processes like short-term habituation.[72,146,147] Thus, parenthetically, this account is also potentially consistent with the central role of PV+ interneurons[148–150] and the hippocampus[151,152] in schizophrenia and its onset.[130,153]

A second important caveat when extrapolating from *Gria1*$^{-/-}$ mice to schizophrenia is that the *GRIA1* locus is but one of many risk genes, each of which in isolation has a very small effect on disease risk. In this respect, it is notable that the recent GWAS study and meta-analysis also implicates other glutamatergic genes, including *GRIN2A*, which encodes the NMDA receptor GluN2A (NR2A) subunit.[34] *Grin2A*$^{-/-}$ mice have a behavioural phenotype similar to that seen in *Gria1*$^{-/-}$ mice, albeit less extensively characterized, including a deficit in short-term habituation. For example, *Grin2A*$^{-/-}$ mice are unable to discriminate between a novel arm and recently experienced, familiar arm during the spatial novelty preference Y-maze test.[154] This is set against an otherwise normal ability to perceive stimuli and to form long-term associations. These *Grin2A* data suggest that our proposal regarding *GRIA1* and its role in short-term habituation

and aberrant salience may generalize to at least some other glutamatergic genes that are involved in schizophrenia, reflecting their convergent effects on pathophysiological processes. As the genomics and genetic architecture of schizophrenia become clearer, it will be of interest to ascertain the identity and nature of the interplay between risk genes, and thence whether there is a functional convergence upon short-term habituation and salience. Such convergence is plausible, given that the underlying neural processes that support short-term habituation likely utilize fundamental synaptic plasticity mechanisms and pathways involving numerous molecular targets.[26–29,155–158]

CONCLUSIONS

We have drawn attention to the impaired short-term habituation phenotype of *Gria1*$^{-/-}$ mice and suggest that this impairment can generate sensitization and aberrant salience, potentially via enhanced dopaminergic signalling and defective hippocampal circuits. Impaired habituation, aberrant salience, hyperdopaminergia and the hippocampus are all central to current models of psychosis. The recent discovery that the *GRIA1* locus shows genome-wide association to schizophrenia suggests that this phenotypic overlap between *Gria1*$^{-/-}$ mice and the clinical syndrome is more than coincidence and instead reflects a pathway of causal significance linking these phenomena in schizophrenia. Indeed, *GRIA1* provides arguably the first clear link between a GWAS-positive finding in schizophrenia and a core psychological process at the heart of the disorder. Clearly, this remains a speculative notion and requires further critical evaluation using a range of approaches. The real value of rodent models in the next decade is surely in this domain: not as models of schizophrenia *per se* but as experimental tools[159] that can help link genomic discoveries to psychological processes and elucidate the underlying neural mechanisms.

CONFLICT OF INTEREST

DMB is a member of the Lilly Centre for Cognitive Neuroscience. The other authors declare no conflict of interest.

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