Disambiguating inhibitory dysfunction in ADHD: Towards the decomposition of developmental brain phenotypes

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In the not too distant past the research consensus was that Attention Deficit/Hyperactivity Disorder (ADHD) is a pathophysiologically homogeneous condition: Localise the site of the core brain deficit shared in common by ADHD patients, we thought, and we will have solved the riddle of the disorder. A number of hypotheses regarding what the core to ADHD might be were proposed. Of these, the notion that ADHD is a disorder of higher order executive control has carried particular weight. Especially influential has been the idea, prefigured in other theories but most effectively crystallized by Barkley(1), that executive dysfunction in ADHD is mediated by alterations in fronto-striatal inhibitory processes. The notion of a common core to ADHD has since been superseded by models of pathophysiological heterogeneity that postulate multiple causal pathways to ADHD each mediated by a different constellation of brain dysfunction(2). In these models inhibitory dysfunction is regarded as underpinning just one of a number of dissociable and different pathways to disorder. Consistent with this, signs of inhibitory deficits on laboratory tasks are found in only a minority (albeit a substantial minority) of patients(3). Even within this sub-group, however, evidence of inhibitory dysfunction needs to be interpreted cautiously given its ambiguity at multiple levels (see table 1).
There is inevitable ambiguity in the ‘read out’ from laboratory-based inhibitory tests as these implicate multiple cognitive and motivational processes (i.e., neuropsychological ambiguity). Apparent inhibitory failure may in fact be due to (i) deficits in more fundamental cognitive functions (4); (ii) inefficient allocation of energetic resources (5) and/or (iii) poor task engagement linked to motivational abnormalities (6). Experimental designs used to disentangle these confounding effects can help to clear up some of this ambiguity. However, in addition, definitive evidence of underlying inhibitory dysfunction requires a shift from the study of behaviour/performance to the study of brain processes. Successful behavioural inhibition may in fact mask underlying abnormalities within inhibitory brain systems as patients either apply additional effort or develop compensatory strategies (7) (i.e., neuro-biological ambiguity). However, establishing inhibitory dysfunction in experimental brain studies still leaves unanswered questions about the causal significance of the revealed deficits (i.e., developmental ambiguity). Inhibitory dysfunction may be core or it may be a secondary effect of earlier neuro-developmental patterns of dysfunction established through the shaping of neural processes by changing patterns of gene expression and experience. Ultimately, therefore, discerning the true significance of neuropsychological measures
of inhibitory dysfunction and their underlying brain correlates requires the study of developmental brain phenotypes in longitudinal designs(8). Two papers in this issue illustrate the potential value of experimental and developmental neuroscience approaches to the study of inhibitory deficits in ADHD.

Doehnart and colleagues (9) carried out a longitudinal study of the electrophysiological markers of attention and inhibitory control deficits in ADHD. Their goal was to test the hypothesis that ADHD is due to a maturational lag in brain development. The study focused on three ERP components each postulated to tap specific anterior and posterior brain networks. At the behavioural level data appeared to support the idea of a general developmental lag. However, ERP data highlighted how potentially misleading relying solely on performance measures can be. ADHD effects may mimic age effects at the level of behaviour or performance but these effects may be unrelated to patterns of neural activation. In fact, in this case, developmental patterns seen for the different ERP components were complex and network specific, with evidence of a developmental lag for some components but not others. Despite obvious ADHD-related abnormalities in the cue P300 (recognised as a marker of attention-related activation in posterior networks) and the CNV (thought to reflect time estimation and
working memory with a combination of anterior and posterior sources) there was little evidence for a developmental lag. Deficits existed but they shared little in common with the pattern of brain activity seen in younger control children. They also remained relatively fixed over the course of the study. In contrast, there was evidence for a developmental lag in the no-go P300, a marker of inhibitory-related brain processes. For this component there was a consistent pattern of deficient activation at all time points during a period of general rapid developmental change seen across the full sample. Furthermore t-maps for the effects of age and ADHD were strikingly similar in terms of the localization of no-go P300 effects. As well as providing some of the first direct evidence in favour of the developmental lag hypothesis (albeit only for certain neuropsychological processes), this study also highlights the value of combining a sophisticated analysis of cognitive processes which distinguishes between specific stimulus-locked ERP components, with longitudinal data to address fundamental questions about the pathogenesis of ADHD.

Groom and colleagues (10), while still focusing on the significance of apparent inhibitory deficits in ADHD, adopted a cross-sectional approach in which they combined experimental methods and brain measurement with a pharmacological probe of
dopamine function (e.g., methylphenidate) to explore the extent to which motivational factors might unpin or at least contribute to apparent inhibitory control deficits in ADHD. The results were complicated and nicely illustrated the importance of experimental, brain-based approaches to inhibitory deficits. Crucially ADHD and controls seemed to perform equally efficiently on the task. However, despite this there was evidence of altered inhibitory-related brain processes as marked by alteration in the P300 and N200 components (although the effects for the N200 component did not reach statistical significance). The appearance of adequate performance on the task masked underlying alterations in inhibitory related anterior brain networks. However, these findings remained somewhat ambiguous. Data on localization of ERPs was not presented nor were analyses conducted for the individual go and the no-go stimulus components. This meant that it remained possible that the alterations in the P300 could be linked to deficient posterior attention networks rather than, or in addition to, the postulated inhibitory deficits in anterior networks. Also the behavioural measure of response inhibition may have been somewhat blunted by the need to equalise the number of correct and incorrect responses using an adjusting procedure. This concern over the sensitivity of the index of behavioural inhibition was reinforced by the finding that the
effects of manipulating motivation and dopamine function (i.e., methylphenidate) could be seen on inhibitory-related ERP measures but not on performance. Crucially, there was little evidence that ADHD-related alterations in brain function were normalised by the use of incentives - N200 and P300 components exhibited by both ADHD and controls were equally affected by either the addition or subtraction of points. More generally this study provided little evidence that participants with ADHD were deficient in processing point-based incentives or that differences in inhibitory-related brain processes in ADHD were caused by such motivational deficit. However, it remains possible that while points are clearly motivating to a degree, for ADHD patients other incentives may be more powerful and their application could differentially reduce the apparent inhibitory deficit seen in this and other studies. For instance, in the delay aversion hypothesis we argue that escape or avoidance of delay is an especially powerful reinforcement for patients with ADHD(11).

These studies using experimental and longitudinal designs represent a crucial initial step in the development of a thoroughgoing experimental developmental neuroscience of ADHD. The ultimate goal of such an enterprise must be to integrate the descriptive study of changes in ADHD-altered brain processes
over time into causal neuro-developmental models of the condition. Such models posit alterations in the underlying neurobiology of ADHD as mediators between originating causes (e.g., genes and environments) and the emergence and persistence of the disorder, processes that are themselves potentially moderated by environmental factors and effects. Such a developmental framework highlights the significance of heterogeneity in neuro-developmental pathways marked by specific brain phenotypes – whereby specific groups of patients within the broader ADHD group can be identified as being distinctive in terms of their longitudinal profile of brain development and the emergence or amelioration of particular patterns of deficit. This heterogeneity represents a fourth level of ambiguity of inhibitory dysfunction in ADHD (i.e., taxonomic ambiguity; see table 1). From this perspective the identification of sub-groups of patients following different neuro-developmental pathways marked by different brain alterations and effects represents a central goal of ADHD science. In order to achieve this goal, large scale longitudinal studies of brain structure and function in ADHD carried out using experimental designs to disentangle confounded processes are required. Advanced statistical tools (such as growth mixture modelling or latent growth curve analysis) can then be used to identify distinctive sub-groups of patients following specific neuro-developmental
pathways. Ultimately it is hoped that such an approach may facilitate the identification of novel treatment targets and promote the development of new and more effective treatments for ADHD(12).

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References


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<th>Level of Ambiguity</th>
<th>Cause</th>
<th>Implications</th>
<th>Scientific Response</th>
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<tr>
<td>Neuropsychological</td>
<td>Inhibitory tasks tap multiple cognitive processes.</td>
<td>It is unclear whether ADHD-control differences reflect - (i) inhibitory dysfunction; (ii) deficits in basic cognitive processes; (iii) altered energetic processes or (iv) lack of motivation and engagement.</td>
<td>Use experimental procedures to disentangle these effects to more precisely specify the source of ADHD –control performance differences.</td>
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<td>Neurobiological</td>
<td>There may be a disconnect between response inhibition performance and the nature of more fundamental alterations in brain processes.</td>
<td>Where ADHD patients perform well on inhibitory tasks this may be masking alterations in more fundamental inhibitory brain processes which may be covered by the application of greater effort or the development of compensatory strategies.</td>
<td>Integrate measures of inhibitory brain processes in studies of response inhibition performance.</td>
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<td>Developmental</td>
<td>Cross sectional studies do not promote an understanding of the full causal significance of inhibitory deficits in ADHD.</td>
<td>Inhibitory deficits, even when validated through the study of brain, may play a secondary role in ADHD pathogenesis being a later effect of earlier established processes.</td>
<td>Conduct longitudinal studies to characterize developmental brain phenotypes relating inhibitory brain processes to more general neuro-developmental pathways.</td>
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<td>Taxonomic</td>
<td>ADHD is a heterogeneous condition - studying developmental brain phenotypes by averaging at the level of the diagnostic group as a whole fails to take account of this.</td>
<td>There are likely to be multiple pathways from originating causes to disorder affecting different sub-groups of patients each mediated by different developmental brain phenotypes some implicating inhibitory dysfunction and some not.</td>
<td>Combine large scale longitudinal studies with advanced statistical approaches such a growth mixture modeling to decompose the performance at the group level into sub-groups with distinct developmental trajectories.</td>
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Table 1: The sources, implications and solutions to the multiple levels of ambiguities identified in inhibitory dysfunction in ADHD.