Frontal release signs and cognition in people with schizophrenia, their siblings and healthy controls

THOMAS M. HYDE, TERRY E. GOLDBERG, MICHAEL F. EGAN, MARC C. LENER and DANIEL R. WEINBERGER

Background Frontal release signs, a subset of neurological soft signs, are common in schizophrenia.

Aims To explore the relationship between frontal release signs and neuropsychological tests of frontal lobe function in people with schizophrenia, their siblings and healthy controls.

Method Neuropsychological tests and frontal release signs were measured in a cohort of index cases (n=302), their siblings (n=240) and healthy controls (n=346).

Results The mean total score of frontal release signs was 1.5 (s.d.=1.58) in the schizophrenia group, 0.54 (s.d.=0.92) for siblings and 0.42 (s.d.=0.77) for controls. Schizophrenia group scores were greater than healthy control or sibling cohort scores (P<0.0001), which did not differ. In all three cohorts, right grasp reflex scores positively correlated with number of perseverative errors on the Wisconsin Card Sort Task (P<0.05). In the schizophrenia group, frontal release signs scores showed an inverse correlation with IQ (R=-0.199, P<0.0005).

Conclusions Our findings of relationships between frontal release signs and cognitive assays of cortical dysfunction and the increased frequency of these signs in people with schizophrenia implicate a cortical origin for these clinical signs and evidence of frontal lobe dysfunction in this disorder.

Declaration of interest None.
extensive battery of neuropsychological tests as described in detail elsewhere (Weickert et al., 2000). These included the short form of the Wechsler Adult Intelligence Scale – Revised (WAIS–R; Wechsler, 1981), a measure of full-scale IQ. The WRAT was administered to assess premorbid IQ. Participants were tested also on a variety of cognitive measures that assess prefrontal function: working memory/executive function was tested with the Wisconsin Card Sorting Test (WCST; Heaton, 1981) and Letter fluency (Benton et al., 1983); psychomotor speed and oculomotor scanning were tested with Trail making test part B (Reitan, 1986); and working memory/updating was tested with the n-back task (Goldberg et al., 2003) (one-back and two-back) (Egan et al., 2001a). Demographic data are presented in Table 1.

Participants underwent a detailed neurological examination by one of two research neuropsychologists who were formally masked to diagnosis and familial relationships. Inter-rater reliability was assessed on 10 participants and revealed that all ratings were significantly correlated (intraclass correlation coefficients 0.54–0.90, P < 0.02). The examination included the Neurological Evaluation Scale (NES; Buchanan & Heinrichs, 1989) scored as previously described (Sanders & Keshavan, 1998). The examiners followed the previously published clinical procedures for assessing each frontal release sign (Paulson & Gottlieb, 1968; Osview, 1997).

Data analyses

The primary outcome measures were the individual and summed frontal release sign scores from the NES (Buchanan & Heinrichs, 1989). For these measures, which are not independent, P = 0.05 was accepted as significant. Data analyses were performed using SAS (version 9.1 for Windows). Mean scores were contrasted by mixed model analysis of variance (ANOVA), treating family status as a random effect. In order to investigate the relationships between frontal release signs and cognitive function, the summed frontal release sign scores were calculated from the individual tests of frontal lobe function from the NES: these included ratings of glabellar, suck, snout, and right and left grasp reflexes. Correlations between averages of the total and individual frontal release sign scores were obtained for each diagnostic group (schizophrenia, sibling and healthy control), using Pearson correlation coefficients. When shared environmental factors are not considered causative of a shared trait in family members, relative risk is commonly thought to reflect shared genetic factors. Relative risk was assessed by comparing the proportion of affected individuals in the sibling cohort v. the proportion of affected individuals in the control cohort (‘affected’ was defined by a summed frontal release sign score greater than 1 standard deviation above the control group mean). A chi-squared analysis was performed to test the significance of the relative risk. As an additional test of possible heritability in sibships, an intraclass correlation coefficient was calculated for total frontal release sign scores.

RESULTS

In the schizophrenia cohort the maximum individual frontal release sign score (on a scale of 0–10) was 7, with an average of 1.50 (s.d. = 1.58). In the control cohort, the maximum score was 4, with a mean of 0.42 (s.d. = 0.77). In the sibling cohort the maximum score was 6, with a mean of 0.54 (s.d. = 0.92) (Fig. 1). Using a mixed model ANOVA, contrasting total frontal release sign scores with diagnostic group, the schizophrenia cohort had significantly higher average scores than the control and sibling cohorts (d.f. = 746; F = 76.26; t = 10.77 and t = 10.52 respectively, P < 0.0001). The control and sibling cohorts did not differ (t = 1.23; P = 0.22). The relative risk was 1.40 (P = 0.25 by χ² analysis), suggesting that frontal release signs are not a strongly familial characteristic in schizophrenia. An alternative method of testing heritability, the intraclass correlation coefficient, was not significant at 0.14 for total frontal release sign score (P = 0.98). The schizophrenia cohort had the greatest number of significant correlations between total and individual frontal release and healthy control), using Pearson correlation coefficients. When shared environmental factors are not considered causative of a shared trait in family members, relative risk is commonly thought to reflect shared genetic factors. Relative risk was assessed by comparing the proportion of affected individuals in the sibling cohort v. the proportion of affected individuals in the control cohort (‘affected’ was defined by a summed frontal release sign score greater than 1 standard deviation above the control group mean). A chi-squared analysis was performed to test the significance of the relative risk. As an additional test of possible heritability in sibships, an intraclass correlation coefficient was calculated for total frontal release sign scores.

RESULTS

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### Table I Demographic characteristics of the sample

<table>
<thead>
<tr>
<th></th>
<th>Study group</th>
<th>Post hoc analysis</th>
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<tbody>
<tr>
<td></td>
<td>Index v. Index v.</td>
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<tr>
<td></td>
<td>Index v. Index v.</td>
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<tr>
<td>Gender</td>
<td></td>
<td>Post hoc analysis</td>
</tr>
<tr>
<td>Male, %</td>
<td>76.8</td>
<td>0.0001</td>
</tr>
<tr>
<td>Education, years: mean (s.d.)</td>
<td>14.0 (2.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>WAIS full-scale IQ: mean (s.d.)</td>
<td>93.0 (12.1)</td>
<td>0.0001</td>
</tr>
<tr>
<td>WRAT (premorbid IQ): mean (s.d.)</td>
<td>102.5 (11.3)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

NS, not significant; WAIS, Wechsler Adult Intelligence Scale; WRAT, Wide Range Achievement Test.

1. Includes participants enrolled full time in college or graduate school.

Fig. 1 The participants with schizophrenia had significantly higher total frontal release sign (FRS) scores than either their siblings or a non-related control group of healthy individuals (error bars represent standard deviations).
Table 2 Correlations between frontal release sign scores and neuropsychological performance in the schizophrenia group

<table>
<thead>
<tr>
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<th>Correlation</th>
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<tbody>
<tr>
<td></td>
<td>Total FRS</td>
</tr>
<tr>
<td>WAIS</td>
<td>-0.199*</td>
</tr>
<tr>
<td>WCST</td>
<td>0.03</td>
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<tr>
<td>One-back</td>
<td>-0.047</td>
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<tr>
<td>Two-back</td>
<td>-0.134</td>
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<tr>
<td>Trails B</td>
<td>0.098</td>
</tr>
<tr>
<td>Letter fluency</td>
<td>-0.116*</td>
</tr>
</tbody>
</table>

FRS, frontal release signs; L, left; R, right; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test.

1. Numbers listed are the r values from the Pearson correlation coefficients between total and individual FRS scores and each neuropsychological test.
2. Percentage perseverative errors.

*P < 0.05.

Table 3 Correlations between frontal release sign scores and neuropsychological performance in the control group

<table>
<thead>
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<th>Correlation</th>
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<tr>
<td>WCST</td>
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<tr>
<td>One-back</td>
<td>-0.066</td>
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<tr>
<td>Two-back</td>
<td>-0.089</td>
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<tr>
<td>Trails B</td>
<td>0.027</td>
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<tr>
<td>Letter fluency</td>
<td>0.038</td>
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</tbody>
</table>

FRS, frontal release signs; L, left; R, right; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test.

*P < 0.05.

Table 4 Correlations between frontal release sign scores and neuropsychological performance in the siblings group

<table>
<thead>
<tr>
<th></th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total FRS</td>
</tr>
<tr>
<td>WAIS</td>
<td>-0.046</td>
</tr>
<tr>
<td>WCST</td>
<td>0.098</td>
</tr>
<tr>
<td>One-back</td>
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<tr>
<td>Two-back</td>
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<tr>
<td>Trails B</td>
<td>0.077</td>
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<tr>
<td>Letter fluency</td>
<td>0.05</td>
</tr>
</tbody>
</table>

FRS, frontal release signs; L, left; R, right; WAIS, Wechsler Adult Intelligence Scale; WCST, Wisconsin Card Sorting Test.

*P < 0.05.

DISCUSSION

Classical clinical–pathological correlations have suggested that frontal release signs in adults are one of the few bedside indices of prefrontal cortical dysfunction. Participants with schizophrenia in our study had a much higher number of frontal release signs on average than controls or their unaffected siblings. This finding is largely in agreement with a number of previous studies (Taylor & Abrams, 1984; Woods et al., 1986; Liddle, 1987; Ismail et al., 1998; Sanders & Keshavan, 1998; Egan et al., 2001b; Lawrie et al., 2001; Cuesta et al., 2002; Gourion et al., 2004). In this study, both individual and summed frontal release sign scores showed weak inverse correlations with several neuropsychological measures, including full-scale IQ, and a positive correlation with number of perseverative errors on the WCST (a test of executive function that reliably engages the dorsolateral prefrontal cortex). These findings were most apparent in the schizophrenia group, perhaps as a result of a greater dynamic range in frontal release sign and cognitive scores.

The greater number of frontal release signs in people with schizophrenia compared with siblings and normal controls was reported previously (Ismail et al., 1998). In fact, a grouping of neurological soft signs that included frontal release signs, abnormalities in eye movements and short-term memory deficits differentiated people with schizophrenia from a healthy control group better than any other sub-scale from the Neurological Evaluation Score (Arango et al., 1999). Both genetic and environmental factors have been cited as the cause of neurological soft signs in schizophrenia; in these studies frontal release signs were subsumed within a larger set of clinical measures (neurological soft signs) and were
Heritability of frontal release signs

There is a suggestion of the heritability of neurological soft signs in general, when studying people with schizophrenia and their non-affected siblings (Egan et al., 2001). However, in this study, they were not examined independently (Ismail et al., 1998; Egan et al., 2001b).

Neurological soft signs previously have been associated with cognitive impairment (Taylor & Abrams, 1984; Liddle, 1987; Schonfeld et al., 1989; Cuesta et al., 2002), including a propensity towards lower IQ (Obiols et al., 1999; Fellick et al., 2001) and a poor long-term functional outcome in first-episode patients (Johnstone et al., 1990). Patients with schizophrenia who had a higher number of soft signs had lower IQ (Kennard, 1960; Mosher et al., 1971; Marcus et al., 1985) and deficits on measures of executive function such as working memory, learning and attention (Saykin et al., 1991; Franke et al., 1992; Braff, 1993; Paulsen et al., 1995). Neuroanatomically, soft signs have been associated with regional grey-matter volume changes that may be an index of perturbed cortical-subcortical connectivity (Dazzan et al., 2004). Although not specific to schizophrenia, neurological soft signs appear to be an intrinsic element of this disorder and have a negative connotation with respect to illness severity.

Frontal release signs and cognitive impairment

In general our correlation between the presence of frontal release signs and poor performance on neuropsychological tests of prefrontal function in schizophrenia agrees with previous reports. However, previous studies differ in some of the details of the findings from our study. One group found that frontal release sign scores correlated with a higher number of random errors but not with perseverative errors on the WCST in people with schizophrenia (Wong et al., 1997). In two studies, global scores of neurological soft signs correlated with perseverative errors on the WCST in schizophrenia, but frontal release signs were not specifically examined (Braun et al., 1995; Mohr et al., 2003). Poor performance by people with schizophrenia on the WCST (as measured by achieved categories) directly correlated with a greater number of neurological soft signs (Bersani et al., 2004). Most studies of frontal release signs have relied upon much smaller samples and therefore have less statistical power than our study. Moreover, most studies of the relationship between neurological abnormalities and prefrontal dysfunction in schizophrenia have not examined frontal release signs separately from other neurological soft signs.

The inverse correlation between full-scale IQ and frontal release signs in schizophrenia is the clearest result in our data. In fact, this is the only correlation that withstands a rigorous Bonferroni correction. This suggests that at least in this sample frontal release signs implicate a more widespread pathology of higher cortical systems. Barnes et al. (1995) measured frontal release sign scores and performance on the WAIS-R in people with schizophrenia: no significant correlation was found, but the total sample size of 48 gave limited power. Two studies have reported an inverse relationship between high scores on more broad-based measures of neurological soft signs and low scores on IQ tests. Neither of these studies evaluated the participants for the presence of frontal release signs; instead, they relied upon other neurological soft signs (Obiols et al., 1999; Fellick et al., 2001). Mohr et al. (2003) found that overall neuropsychological performance inversely correlated with the total score on a battery of neurological soft signs. However, that study did not assay frontal release signs. They did note that higher soft sign scores inversely correlated with a number of sub-tests from the WAIS-R. In general, our findings agree with these previous reports.

Side-effects of antipsychotics might account for our findings. However, similar neurological abnormalities have been noted in schizophrenia for nearly a century, decades before the introduction of antipsychotic therapy (Bleuler, 1950; Kraepelin, 1971). Other studies support the notion that neurological soft signs are an intrinsic part of schizophrenia rather than a direct or indirect consequence of treatment (Johnstone et al., 1990; Gupta et al., 1995; Browne et al., 2000; Mohr et al., 2003; Dazzan et al., 2004). Neurological soft signs and frontal release signs are common in first-episode schizophrenia (Browne et al., 2000); in fact it has been reported that frontal release signs are more common in people with schizophrenia who have never been treated with antipsychotics than in treated patients (Gupta et al., 1995). In addition, unmedicated participants at high risk of schizophrenia have more neurological soft signs than healthy control individuals (Lawrie et al., 2001). These findings suggest that exposure to antipsychotics is not necessary for the appearance of neurological soft signs in general and frontal release signs in particular. In addition, both typical (Mishara & Goldberg, 2004) and atypical (Weickert et al., 2003) antipsychotics may sometimes improve cognitive performance,
militating against antipsychotics as a cause. As a whole, the preponderance of the findings in the psychiatric literature makes it highly unlikely that the findings in our study are solely directly attributable to the deleterious effects of antipsychotic medications.

In summary, people with schizophrenia had more frontal release signs than their siblings or the control group. In the schizophrenia group both individual and summed frontal release sign scores inversely correlated with several neuropsychological measures, including full-scale IQ and the number of perseverative errors on the WCST (a relatively selective test of prefrontal function). Although these findings were most apparent in the participants with schizophrenia, perhaps as a result of a greater range in frontal release sign scores, a trend for similar relationships was also seen in the control group. This suggests that frontal release signs are at best a weak index of prefrontal cognitive dysfunction, particularly in schizophrenia, but also in healthy individuals.

ACKNOWLEDGEMENTS

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REFERENCES


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